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(54) Title: SULFONAMIDE INHIBITORS OF ASPARTYL PROTEASE

## (57) Abstract

The present invention relates to a novel class of sulfonamides which are aspartyl protease inhibitors. In one embodiment, this invention relates to a novel class of HIV aspartyl protease inhibitors characterized by specific structural and physicochemical features. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting HIV-1 and HIV-2 protease activity and consequently, may be advantageously used as anti-viral agents against the HIV-1 and HIV-2 viruses. This invention also relates to methods for inhibiting the activity of HIV aspartyl protease using the compounds of this invention and methods for screening compounds for anti-HIV activity.

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SULFONAMIDE INHIBITORS OF ASPARTYL PROTEASE

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TECHNICAL FIELD OF THE INVENTION

The present invention relates to a novel class of sulfonamides which are aspartyl protease inhibitors. In one embodiment, this invention relates to a novel class of HIV 10 aspartyl protease inhibitors characterized by specific structural and physicochemical features. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting 15 HIV-1 and HIV-2 protease activity and consequently, may be advantageously used as anti-viral agents against the HIV-1 and HIV-2 viruses. This invention also relates to methods for inhibiting the activity of HIV aspartyl protease using the compounds of this invention and methods for screening 20 compounds for anti-HIV activity.

BACKGROUND OF THE INVENTION

The human immunodeficiency virus ("HIV") is the causative agent for acquired immunodeficiency syndrome 25 ("AIDS") -- a disease characterized by the destruction of the immune system, particularly of CD4<sup>+</sup> T-cells, with attendant susceptibility to opportunistic infections -- and its precursor AIDS-related complex ("ARC") -- a syndrome characterized by symptoms such as persistent generalized 30 lymphadenopathy, fever and weight loss.

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As in the case of several other retroviruses, HIV encodes the production of a protease which carries out post-translational cleavage of precursor polypeptides in a process necessary for the formation of infectious virions

5 (S. Crawford et al., "A Deletion Mutation in the 5' Part of the pol Gene of Moloney Murine Leukemia Virus Blocks Proteolytic Processing of the gag and pol Polyproteins", J. Virol., 53, p. 899 (1985)). These gene products include pol, which encodes the virion RNA-dependent DNA polymerase

10 (reverse transcriptase), an endonuclease, HIV protease, and gag, which encodes the core-proteins of the virion (H. Toh et al., "Close Structural Resemblance Between Putative Polymerase of a Drosophila Transposable Genetic Element 17.6 and pol gene product of Moloney Murine Leukemia Virus",

15 EMBO J., 4, p. 1267 (1985); L.H. Pearl et al., "A Structural Model for the Retroviral Proteases", Nature, pp. 329-351 (1987); M.D. Power et al., "Nucleotide Sequence of SRV-1, a Type D Simian Acquired Immune Deficiency Syndrome Retrovirus", Science, 231, p. 1567 (1986)).

20 A number of synthetic anti-viral agents have been designed to target various stages in the replication cycle of HIV. These agents include compounds which block viral binding to CD4' T-lymphocytes (for example, soluble CD4), and compounds which interfere with viral replication by

25 inhibiting viral reverse transcriptase (for example, didanosine and zidovudine (AZT)) and inhibit integration of viral DNA into cellular DNA (M.S. Hirsh and R.T. D'Aquila, "Therapy for Human Immunodeficiency Virus Infection", New Eng. J. Med., 328, p. 1686 (1993)). However, such agents,

30 which are directed primarily to early stages of viral replication, do not prevent the production of infectious virions in chronically infected cells. Furthermore, administration of some of these agents in effective amounts

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has led to cell-toxicity and unwanted side effects, such as anemia and bone marrow suppression.

More recently, the focus of anti-viral drug design has been to create compounds which inhibit the formation of infectious virions by interfering with the processing of viral polyprotein precursors. Processing of these precursor proteins requires the action of virus-encoded proteases which are essential for replication (Kohl, N.E. et al.

"Active HIV Protease is Required for Viral Infectivity"

10 Proc. Natl. Acad. Sci. USA, 85, p. 4686 (1988)). The anti-viral potential of HIV protease inhibition has been demonstrated using peptidal inhibitors. Such peptidal compounds, however, are typically large and complex molecules that tend to exhibit poor bioavailability and are

15 not generally consistent with oral administration.

Accordingly, the need still exists for compounds that can effectively inhibit the action of viral proteases, for use as agents for preventing and treating chronic and acute viral infections.

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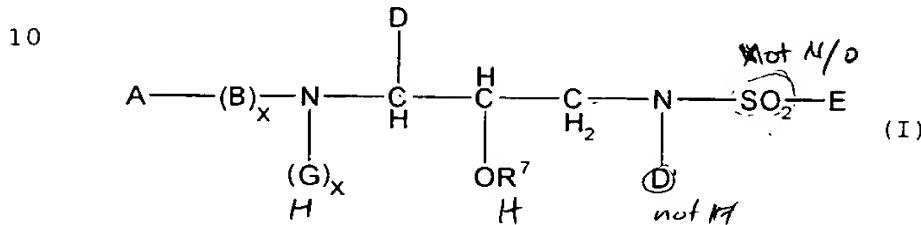
#### SUMMARY OF THE INVENTION

The present invention provides a novel class of compounds, and pharmaceutically acceptable derivatives thereof, that are useful as inhibitors of aspartyl proteases, in particular, HIV aspartyl protease. These compounds can be used alone or in combination with other therapeutic or prophylactic agents, such as anti-virals, antibiotics, immunomodulators or vaccines, for the treatment or prophylaxis of viral infection.

30 According to a preferred embodiment, the compounds of this invention are capable of inhibiting HIV viral replication in human CD<sub>4</sub> T-cells. These compounds are useful as therapeutic and prophylactic agents to treat or prevent infection by HIV-1 and related viruses which may

result in asymptomatic infection, AIDS-related complex ("ARC"), acquired immunodeficiency syndrome ("AIDS"), or similar disease of the immune system.

It is a principal object of this invention to provide a novel class of sulfonamides which are aspartyl protease inhibitors, and particularly, HIV aspartyl protease inhibitors. The novel sulfonamides of this invention are those of formula I:



15 wherein:

A is selected from H; Ht;  $-R^1-Ht$ ;  $-R^1-C_1-C_6$  alkyl, which is optionally substituted with one or more groups independently selected from hydroxy,  $C_1-C_4$  alkoxy, Ht,  $-O-Ht$ ,  $-NR^2-CO-N(R^2)_2$ ; or  $-CO-N(R^2)_2$ ;  $-R^1-C_2-C_6$  alkenyl, which is optionally substituted with one or more groups independently selected from hydroxy,  $C_1-C_4$  alkoxy, Ht,  $-O-Ht$ ,  $-NR^2-CO-N(R^2)_2$  or  $-CO-N(R^2)_2$ ; or  $R^7$ ;

20 each  $R^1$  is independently selected from  $-C(O)-$ ,  $-S(O)_2-$ ,  $-C(O)-C(O)-$ ,  $-O-C(O)-$ ,  $-O-S(O)_2-$ ,  $-NR^2-S(O)_2-$ ,  $-NR^2-C(O)-$  or  $-NR^2-C(O)-C(O)-$ ;

25 each Ht is independently selected from  $C_3-C_7$  cycloalkyl;  $C_5-C_7$  cycloalkenyl;  $C_6-C_{14}$  aryl; or a 5-7 membered saturated or unsaturated heterocycle, containing one or more heteroatoms selected from N,  $N(R^2)$ , O, S and  $S(O)_n$ ; wherein said aryl or said heterocycle is optionally fused to Q; and wherein any member of said Ht is optionally substituted with one or more substituents independently selected from oxo,  $-OR^2$ ,  $SR^2$ ,  $-R^2$ ,  $-N(R^2)(R^2)$ ,  $-R^2-OH$ ,  $-CN$ ,  $-CO_2R^2$ ,  $-C(O)-N(R^2)_2$ ,  $-S(O)_2-N(R^2)_2$ ,  $-N(R^2)-C(O)-R^2$ ,  $-C(O)-R^2$ ,

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-S(O)<sub>n</sub>-R<sup>2</sup>, -OCF<sub>3</sub>, -S(O)<sub>n</sub>-Q, methylenedioxy, -N(R<sup>2</sup>)-S(O)<sub>2</sub>(R<sup>2</sup>), halo, -CF<sub>3</sub>, -NO<sub>2</sub>, Q, -OQ, -OR<sup>7</sup>, -SR<sup>7</sup>, -R<sup>7</sup>, -N(R<sup>2</sup>)(R<sup>7</sup>) or -N(R<sup>7</sup>)<sub>2</sub>;

each R<sup>2</sup> is independently selected from H, or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with Q or R<sup>10</sup>;

B, when present, is -N(R<sup>2</sup>)-C(R<sup>3</sup>)<sub>2</sub>-C(O)-;

each x is independently 0 or 1;

each R<sup>3</sup> is independently selected from H, Ht, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl or C<sub>5</sub>-C<sub>6</sub> cycloalkenyl;

wherein any member of said R<sup>3</sup>, except H, is optionally substituted with one or more substituents selected from -OR<sup>2</sup>, -C(O)-NH-R<sup>2</sup>, -S(O)<sub>n</sub>-N(R<sup>2</sup>)(R<sup>2</sup>), Ht, -CN, -SR<sup>2</sup>, -CO<sub>2</sub>R<sup>2</sup>, NR<sup>2</sup>-C(O)-R<sup>2</sup>;

each n is independently 1 or 2;

G, when present, is selected from H, R<sup>7</sup> or C<sub>1</sub>-C<sub>4</sub> alkyl, or, when G is C<sub>1</sub>-C<sub>4</sub> alkyl, G and R<sup>7</sup> are bound to one another either directly or through a C<sub>1</sub>-C<sub>3</sub> linker to form a heterocyclic ring; or

when G is not present (i.e., when x in (G)<sub>x</sub> is 0), then the nitrogen to which G is attached is bound directly to the R<sup>7</sup> group in -OR<sup>7</sup> with the concomitant displacement of one -ZM group from R<sup>7</sup>;

D is selected from Q; C<sub>1</sub>-C<sub>6</sub> alkyl, which is optionally substituted with one or more groups selected from C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -OR<sup>2</sup>, -S-Ht, -R<sup>3</sup>, -O-Q or Q; C<sub>2</sub>-C<sub>4</sub> alkenyl, which is optionally substituted with one or more groups selected from -OR<sup>2</sup>, -S-Ht, -R<sup>3</sup>, -O-Q or Q; C<sub>3</sub>-C<sub>6</sub> cycloalkyl, which is optionally substituted with or fused to Q; or C<sub>5</sub>-C<sub>6</sub> cycloalkenyl, which is optionally substituted with or fused to Q;

each Q is independently selected from a 3-7 membered saturated, partially saturated or unsaturated carbocyclic ring system; or a 5-7 membered saturated, partially saturated or unsaturated heterocyclic ring

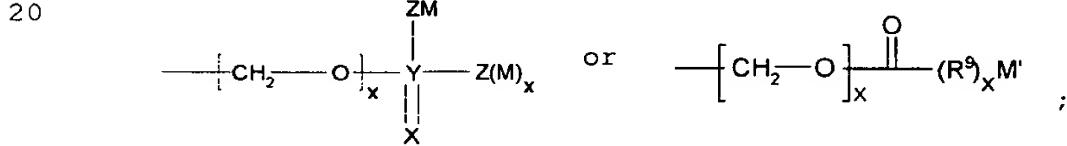
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containing one or more heteroatoms selected from O, N, S, S(O)<sub>n</sub> or N(R<sup>2</sup>); wherein Q is optionally substituted with one or more groups selected from oxo, -OR<sup>1</sup>, -R<sup>2</sup>, -SO<sub>2</sub>R<sup>2</sup>, -SO<sub>2</sub>-N(R<sup>2</sup>)<sub>2</sub>, -N(R<sup>2</sup>)<sub>2</sub>, -N(R<sup>2</sup>)-C(O)-R<sup>2</sup>, -R<sup>2</sup>-OH, -CN, -CO<sub>2</sub>R<sup>2</sup>, -C(O)-N(R<sup>2</sup>)<sub>2</sub>, halo or -CF<sub>3</sub>;

5 D' is selected from -OR<sup>10</sup>, -N=R<sup>10</sup> or -N(R<sup>10</sup>)-R<sup>1</sup>-R<sup>3</sup>;  
 E is selected from Ht; O-Ht; Ht-Ht; -O-R<sup>3</sup>;  
 -N(R<sup>2</sup>)(R<sup>3</sup>); C<sub>1</sub>-C<sub>6</sub> alkyl, which is optionally substituted with one or more groups selected from R<sup>4</sup> or Ht; C<sub>2</sub>-C<sub>6</sub> alkenyl,  
 10 which is optionally substituted with one or more groups selected from R<sup>4</sup> or Ht; C<sub>3</sub>-C<sub>6</sub> saturated carbocycle, which is optionally substituted with one or more groups selected from R<sup>4</sup> or Ht; or C<sub>5</sub>-C<sub>6</sub> unsaturated carbocycle, which is optionally substituted with one or more groups selected from R<sup>4</sup> or Ht;

15 each R<sup>4</sup> is independently selected from -OR<sup>2</sup>, -SR<sup>2</sup>, -SOR<sup>2</sup>, -SO<sub>2</sub>R<sup>2</sup>, -CO<sub>2</sub>R<sup>2</sup>, -C(O)-NHR<sup>2</sup>, -C(O)-N(R<sup>2</sup>)<sub>2</sub>, -C(O)-NR<sup>2</sup>(OR<sup>2</sup>), -S(O)<sub>2</sub>-NHR<sup>2</sup>, halo, -NR<sup>2</sup>-C(O)-R<sup>2</sup>, -N(R<sup>2</sup>)<sub>2</sub> or -CN;

each R<sup>7</sup> is independently selected from hydrogen,



wherein each M is independently selected  
 25 from H, Li, Na, K, Mg, Ca, Ba, -N(R<sup>2</sup>)<sub>4</sub>, C<sub>1</sub>-C<sub>12</sub>-alkyl, C<sub>2</sub>-C<sub>12</sub>-alkenyl, or -R<sup>6</sup>; wherein 1 to 4 -CH<sub>2</sub> radicals of the alkyl or alkenyl group, other than the -CH<sub>2</sub> that is bound to Z, is optionally replaced by a heteroatom group selected from O, S, S(O), S(O<sub>2</sub>), or N(R<sup>2</sup>); and wherein any hydrogen in said  
 30 alkyl, alkenyl or R<sup>6</sup> is optionally replaced with a substituent selected from oxo, -OR<sup>2</sup>, -R<sup>2</sup>, N(R<sup>2</sup>)<sub>2</sub>, N(R<sup>2</sup>)<sub>3</sub>, R<sup>2</sup>OH, -CN, -CO<sub>2</sub>R<sup>2</sup>, -C(O)-N(R<sup>2</sup>)<sub>2</sub>, S(O)<sub>2</sub>-N(R<sup>2</sup>)<sub>2</sub>, N(R<sup>2</sup>)-C(O)-R<sub>2</sub>, C(O)R<sup>2</sup>, -S(O)<sub>n</sub>-R<sup>2</sup>, OCF<sub>3</sub>, -S(O)<sub>n</sub>-R<sup>6</sup>, N(R<sup>2</sup>)-S(O)<sub>2</sub>(R<sup>2</sup>), halo, -CF<sub>3</sub>, or -NO<sub>2</sub>;

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M' is H, C<sub>1</sub>-C<sub>12</sub>-alkyl, C<sub>2</sub>-C<sub>12</sub>-alkenyl, or -R<sup>6</sup>;  
 wherein 1 to 4 -CH<sub>2</sub> radicals of the alkyl or alkenyl group  
 is optionally replaced by a heteroatom group selected from  
 O, S, S(O), S(O<sub>2</sub>), or N(R<sup>2</sup>); and wherein any hydrogen in  
 5 said alkyl, alkenyl or R<sup>6</sup> is optionally replaced with a  
 substituent selected from oxo, -OR<sup>2</sup>, -R<sup>2</sup>, -N(R<sup>2</sup>)<sub>2</sub>, N(R<sup>2</sup>)<sub>3</sub>,  
 -R<sup>2</sup>OH, -CN, -CO<sub>2</sub>R<sup>2</sup>, -C(O)-N(R<sup>2</sup>)<sub>2</sub>, -S(O)<sub>2</sub>-N(R<sup>2</sup>)<sub>2</sub>,  
 -N(R<sup>2</sup>)-C(O)-R<sub>2</sub>, -C(O)R<sup>2</sup>, -S(O)<sub>n</sub>-R<sup>2</sup>, -OCF<sub>3</sub>, -S(O)<sub>n</sub>-R<sup>6</sup>,  
 -N(R<sup>2</sup>)-S(O)<sub>2</sub>(R<sup>2</sup>), halo, -CF<sub>3</sub>, or -NO<sub>2</sub>;

10 Z is O, S, N(R<sup>2</sup>)<sub>2</sub>, or, when M is not present, H.  
 Y is P or S;  
 X is O or S; and  
 R<sup>2</sup> is C(R<sup>2</sup>)<sub>2</sub>, O or N(R<sup>2</sup>); and wherein when Y is S,  
 Z is not S; and

15 R<sup>6</sup> is a 5-6 membered saturated, partially  
 saturated or unsaturated carbocyclic or heterocyclic ring  
 system, or an 8-10 membered saturated, partially saturated  
 or unsaturated bicyclic ring system; wherein any of said  
 heterocyclic ring systems contains one or more heteroatoms  
 20 selected from O, N, S, S(O)<sub>n</sub> or N(R<sup>2</sup>); and wherein any of  
 said ring systems optionally contains 1 to 4 substituents  
 independently selected from OH, C<sub>1</sub>-C<sub>4</sub> alkyl, -O-C<sub>1</sub>-C<sub>4</sub> alkyl  
 or -O-C(O)-C<sub>1</sub>-C<sub>4</sub> alkyl;

25 R<sup>10</sup> is selected from C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>6</sub>-C<sub>14</sub>  
 aryl or Ht, wherein R<sup>10</sup> optionally contains up to three  
 substituents independently selected from -R<sup>3</sup>, -CN, -SR<sup>5</sup>,  
 -SOR<sup>5</sup>, -SO<sub>2</sub>R<sup>5</sup>, -SR-NR<sup>5</sup>-C(O)R<sup>6</sup>, -NR<sup>5</sup>-(SO<sub>2</sub>)R<sup>5</sup>, -C(O)N(R<sup>5</sup>)<sub>2</sub>,  
 -C(S)N(R<sup>5</sup>)<sub>2</sub>, -S(O)<sub>2</sub>N(R<sup>5</sup>)<sub>2</sub>, -C(O)R<sup>6</sup>, -C(S)R<sup>6</sup>, -N(R<sup>5</sup>)<sub>2</sub>, -NR<sup>5</sup>-  
 C(O)R<sup>5</sup>, -NR<sup>5</sup>-C(O)OR<sup>5</sup>, -NR<sup>5</sup>-C(O)N(R<sup>5</sup>)<sub>2</sub>, -NR<sup>5</sup>-C(S)R<sup>5</sup>, -NR<sup>5</sup>-  
 30 C(S)OR<sup>5</sup>, -NR<sup>5</sup>-C(S)N(R<sup>5</sup>)<sub>2</sub>, -NR<sup>5</sup>-C[=N(R<sup>5</sup>)]-N(R<sup>5</sup>)<sub>2</sub>, -NH-C[=N-NO<sub>2</sub>]-  
 NH<sub>2</sub>, -NH-C[=N-NO<sub>2</sub>]-OR<sup>5</sup>, -N(R<sup>8</sup>)<sub>2</sub>-C(O)R<sup>8</sup>, -OC(O)R<sup>6</sup>,  
 -OC(O)N(R<sup>5</sup>)<sub>2</sub>, -OC(S)N(R<sup>5</sup>)<sub>2</sub>, wherein any one of the -CH<sub>2</sub>  
 groups of said alkyl or alkenyl chains of R<sup>10</sup> may be  
 optionally replaced by O, S, SO, SO<sub>2</sub>, C(O) or NR<sup>5</sup>;

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wherein each R<sup>5</sup> is independently selected from hydrogen, C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>8</sub> alkenyl, C<sub>2</sub>-C<sub>8</sub> alkynyl or Ht, wherein each R<sup>5</sup>, except for hydrogen, is optionally substituted with -CF<sub>3</sub>, -PO<sub>3</sub>R<sup>3</sup>, azido or halo.

5        It is also an object of this invention to provide pharmaceutical compositions comprising the sulfonamides of formula (I) and methods for their use as inhibitors of HIV aspartyl protease.

10        DETAILED DESCRIPTION OF THE INVENTION

In order that the invention herein described may be more fully understood, the following detailed description is set forth. In the description, the following terms are employed herein:

15        Unless expressly stated to the contrary, the terms "-SO<sub>2</sub>-" and "-S(O)<sub>2</sub>-" as used herein refer to a sulfone or sulfone derivative (i.e., both appended groups linked to the S), and not a sulfinate ester.

20        For the compounds of formula I, and intermediates thereof, the stereochemistry of OR<sup>7</sup> is defined relative to D on the adjacent carbon atom, when the molecule is drawn in an extended zig-zag representation (such as that drawn for compound of formula I). If both OR<sup>7</sup> and D reside on the same side of the plane defined by the extended backbone of 25 the compound, the stereochemistry of OR<sup>7</sup> will be referred to as "syn". If OR<sup>7</sup> and D reside on opposite sides of that plane, the stereochemistry of OR<sup>7</sup> will be referred to as "anti".

30        The term "alkyl", alone or in combination with any other term, refers to a straight-chain or branch-chain saturated aliphatic hydrocarbon radical containing the specified number of carbon atoms, or where no number is specified, preferably from 1 to about 10 and more preferably from 1 to about 8 carbon atoms. Examples of alkyl radicals

include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, n-hexyl and the like.

5 The term "alkenyl" alone or in combination with any other term, refers to a straight-chain or branched-chain mono- or poly-unsaturated aliphatic hydrocarbon radical containing the specified number of carbon atoms, or where no number is specified, preferably from 2 to about 18 carbon  
10 atoms and more preferably, from 2 to about 8 carbon atoms. Examples of alkenyl radicals include, but are not limited to, ethenyl, propenyl, isopropenyl, 1,4-butadienyl, pentenyl and the like.

15 The term "alkoxy" refers to an alkyl ether radical, wherein the term "alkyl" is defined above. Examples of suitable alkyl ether radicals include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy and the like.

20 The term "aryl" alone or in combination with any other term, refers to a carbocyclic aromatic radical (such as phenyl or naphthyl) containing the specified number of carbon atoms, preferably from 6-14 carbon atoms, and more  
25 preferably from 6-10 carbon atoms, optionally substituted with one or more substituents selected from C1-6 alkoxy, (for example methoxy), nitro, halogen, (for example chloro), amino, carboxylate and hydroxy. Examples of aryl radicals include, but are not limited to phenyl, naphthyl, indenyl,  
30 indanyl, azulenyl, fluorenyl, anthracenyl and the like.

The term "heterocyclyl" or "heterocycle" refers to a stable 3-7 membered monocyclic heterocyclic ring or 8-11 membered bicyclic heterocyclic ring which is either

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saturated or unsaturated, and which may be optionally benzofused if monocyclic. Each heterocycle consists of one or more carbon atoms and from one to four heteroatoms selected from the group consisting of nitrogen, oxygen and 5 sulfur. As used herein, the terms "nitrogen and sulfur heteroatoms" include any oxidized form of nitrogen and sulfur, and the quaternized form of any basic nitrogen. A heterocyclyl radical may be attached at any endocyclic carbon or heteroatom which results in the creation of a 10 stable structure. Preferred heterocycles include 5-7 membered monocyclic heterocycles and 8-10 membered bicyclic heterocycles. Examples of such groups include imidazolyl, imidazolinoyl, imidazolidinyl, quinolyl, isoquinolyl, indolyl, indazolyl, indazolinolyl, perhydropyridazyl, 15 pyridazyl, pyridyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazinyl, quinoxolyl, piperidinyl, pyranyl, pyrazolinyl, piperazinyl, pyrimidinyl, pyridazinyl, morpholinyl, thiamorpholinyl, furyl, thienyl, triazolyl, thiazolyl, carbolinyl, tetrazolyl, thiazolidinyl, 20 benzofuranoyl, thiamorpholinyl sulfone, oxazolyl, benzoxazolyl, oxopiperidinyl, oxopyrrolidinyl, oxoazepinyl, azepinyl, isoxozolyl, isothiazolyl, furazanyl, tetrahydropyranyl, tetrahydrofuranyl, thiazolyl, thiadiazoyl, dioxolyl, dioxinyl, oxathiolyl, benzodioxolyl, 25 dithioly, thiophenyl, tetrahydrothiophenyl, sulfolanyl, dioxanyl, dioxolanyl, tetrahydrofurodihydrofuranyl, tetrahydropyranodihydrofuranyl, dihydropyranyl, tetradyrofurofuranyl and tetracydropyranofuranyl.

30 The term "pharmaceutically effective amount" refers to an amount effective in treating a virus infection, for example an HIV infection, in a patient either as monotherapy or in combination with other agents. The term "treating" as used herein refers to the alleviation of

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symptoms of a particular disorder in a patient or the improvement of an ascertainable measurement associated with a particular disorder. The term "prophylactically effective amount" refers to an amount effective in preventing a virus 5 infection, for example an HIV infection, in a patient. As used herein, the term "patient" refers to a mammal, including a human.

The terms "HIV protease" and "HIV aspartyl 10 protease" are used interchangeably and refer to the aspartyl protease encoded by the human immunodeficiency virus type 1 or 2. In a preferred embodiment of this invention, these terms refer to the human immunodeficiency virus type 1 aspartyl protease.

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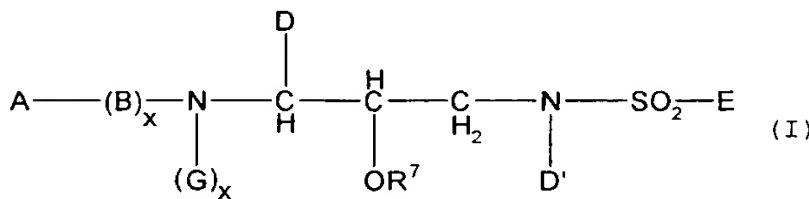
The term "thiocarbamates" refers to compounds containing the functional group N-SO<sub>2</sub>-O.

Combinations of substituents and variables 20 envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and administration to a mammal by methods known in the art. Typically, such 25 compounds are stable at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds 30 disclosed herein. The basic nitrogen can be quaternized with any agents known to those of ordinary skill in the art including, for example, lower alkyl halides, such as methyl, ethyl, propyl and butyl chloride, bromides and iodides; dialkyl sulfates including dimethyl, diethyl, dibutyl and

10 diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aralkyl halides including benzyl and phenethyl bromides. Water or oil-soluble or dispersible products may be obtained  
5 by such quaternization.

15 The novel 'sulfonamides of this invention are those of formula I:



15 wherein:

20 A is selected from H; Ht;  $-R^1$ -Ht;  $-R^1-C_1-C_6$  alkyl, which is optionally substituted with one or more groups independently selected from hydroxy,  $C_1-C_4$  alkoxy, Ht,  $-O$ -Ht,  $-NR^2-CO-N(R^2)_2$  or  $-CO-N(R^2)_2$ ;  $-R^1-C_2-C_6$  alkenyl, which is optionally substituted with one or more groups independently selected from hydroxy,  $C_1-C_4$  alkoxy, Ht,  $-O$ -Ht,  $-NR^2-CO-N(R^2)_2$  or  $-CO-N(R^2)_2$ ; or  $R^7$ ;

25 each  $R^1$  is independently selected from  $-C(O)-$ ,  $-S(O)_2-$ ,  $-C(O)-C(O)-$ ,  $-O-C(O)-$ ,  $-O-S(O)_2-$ ,  $-NR^2-S(O)_2-$ ,  $-NR^2-C(O)-$  or  $-NR^2-C(O)-C(O)-$ ;

30 each Ht is independently selected from  $C_3-C_7$  cycloalkyl;  $C_5-C_7$  cycloalkenyl;  $C_6-C_{14}$  aryl; or a 5-7 membered saturated or unsaturated heterocycle, containing one or more heteroatoms selected from N,  $N(R^2)$ , O, S and  $S(O)_n$ ; wherein said aryl or said heterocycle is optionally fused to Q; and wherein any member of said Ht is optionally substituted with one or more substituents independently selected from oxo,  $-OR^2$ ,  $SR^2$ ,  $-R^2$ ,  $-N(R^2)(R^2)$ ,  $-R^2-OH$ ,  $-CN$ ,  $-CO_2R^2$ ,  $-C(O)-N(R^2)_2$ ,  $-S(O)_2-N(R^2)_2$ ,  $-N(R^2)-C(O)-R^2$ ,  $-C(O)-R^2$ ,

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-S(O)<sub>n</sub>-R<sup>2</sup>, -OCF<sub>3</sub>, -S(O)<sub>n</sub>-Q, methylenedioxy, -N(R<sup>2</sup>)-S(O)<sub>2</sub>(R<sup>2</sup>), halo, -CF<sub>3</sub>, -NO<sub>2</sub>, Q, -OQ, -OR<sup>7</sup>, -SR<sup>7</sup>, -R<sup>7</sup>, -N(R<sup>2</sup>)(R<sup>7</sup>) or -N(R<sup>7</sup>)<sub>2</sub>;

each R<sup>2</sup> is independently selected from H, or C<sub>1</sub>-C<sub>6</sub> alkyl optionally substituted with Q or R<sup>10</sup>;

B, when present, is -N(R<sup>2</sup>)-C(R<sup>3</sup>)<sub>2</sub>-C(O)-;

each x is independently 0 or 1;

each R<sup>3</sup> is independently selected from H, Ht, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl or C<sub>5</sub>-C<sub>6</sub> cycloalkenyl; 10 wherein any member of said R<sup>3</sup>, except H, is optionally substituted with one or more substituents selected from -OR<sup>2</sup>, -C(O)-NH-R<sup>2</sup>, -S(O)<sub>n</sub>-N(R<sup>2</sup>)(R<sup>2</sup>), Ht, -CN, -SR<sup>2</sup>, -CO<sub>2</sub>R<sup>2</sup>, NR<sup>2</sup>-C(O)-R<sup>2</sup>;

each n is independently 1 or 2;

15 G, when present, is selected from H, R<sup>7</sup> or C<sub>1</sub>-C<sub>4</sub> alkyl, or, when G is C<sub>1</sub>-C<sub>4</sub> alkyl, G and R<sup>7</sup> are bound to one another either directly or through a C<sub>1</sub>-C<sub>3</sub> linker to form a heterocyclic ring; or

when G is not present (i.e., when x in (G)<sub>x</sub> is 0), 20 then the nitrogen to which G is attached is bound directly to the R<sup>7</sup> group in -OR<sup>7</sup> with the concomitant displacement of one -ZM group from R<sup>7</sup>;

D is selected from Q; C<sub>1</sub>-C<sub>6</sub> alkyl, which is 25 optionally substituted with one or more groups selected from C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -OR<sup>2</sup>, -S-Ht, -R<sup>3</sup>, -O-Q or Q; C<sub>2</sub>-C<sub>4</sub> alkenyl, which is optionally substituted with one or more groups selected from -OR<sup>2</sup>, -S-Ht, -R<sup>3</sup>, -O-Q or Q, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, which is optionally substituted with or fused to Q; or C<sub>5</sub>-C<sub>6</sub> cycloalkenyl, which is optionally substituted with or fused 30 to Q;

each Q is independently selected from a 3-7 membered saturated, partially saturated or unsaturated carbocyclic ring system; or a 5-7 membered saturated, partially saturated or unsaturated heterocyclic ring

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containing one or more heteroatoms selected from O, N, S, S(O)<sub>n</sub> or N(R<sup>2</sup>); wherein Q is optionally substituted with one or more groups selected from oxo, -OR<sup>2</sup>, -R<sup>2</sup>, -SO<sub>2</sub>R<sup>2</sup>, -SO<sub>2</sub>-N(R<sup>2</sup>)<sub>2</sub>, -N(R<sup>2</sup>)<sub>2</sub>, -N(R<sup>2</sup>)-C(O)-R<sup>2</sup>, -R<sup>2</sup>-OH, -CN, -CO<sub>2</sub>R<sup>2</sup>, 5 -C(O)-N(R<sup>2</sup>)<sub>2</sub>, halo or -CF<sub>3</sub>;

D' is selected from -OR<sup>10</sup>, -N=R<sup>10</sup> or -N(R<sup>10</sup>)-R<sup>1</sup>-R<sup>3</sup>;

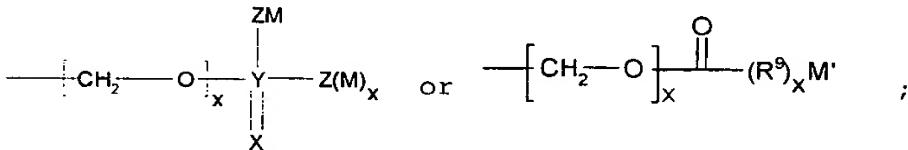
E is selected from Ht; O-Ht; Ht-Ht; -O-R<sup>3</sup>; -N(R<sup>2</sup>)(R<sup>3</sup>); C<sub>1</sub>-C<sub>6</sub> alkyl, which is optionally substituted with one or more groups selected from R<sup>4</sup> or Ht; C<sub>2</sub>-C<sub>6</sub> alkenyl,

10 which is optionally substituted with one or more groups selected from R<sup>4</sup> or Ht; C<sub>3</sub>-C<sub>6</sub> saturated carbocycle, which is optionally substituted with one or more groups selected from R<sup>4</sup> or Ht; or C<sub>5</sub>-C<sub>6</sub> unsaturated carbocycle, which is optionally substituted with one or more groups selected from 15 R<sup>4</sup> or Ht;

each R<sup>4</sup> is independently selected from -OR<sup>2</sup>, -SR<sup>2</sup>, -SOR<sup>2</sup>, -SO<sub>2</sub>R<sup>2</sup>, -CO<sub>2</sub>R<sup>2</sup>, -C(O)-NHR<sup>2</sup>, -C(O)-N(R<sup>2</sup>)<sub>2</sub>, -C(O)-NR<sup>2</sup>(OR<sup>2</sup>), -S(O)<sub>2</sub>-NHR<sup>2</sup>, halo, -NR<sup>2</sup>-C(O)-R<sup>2</sup>, -N(R<sup>2</sup>)<sub>2</sub> or -CN;

each R<sup>7</sup> is independently selected from hydrogen,

20



wherein each M is independently selected

25 from H, Li, Na, K, Mg, Ca, Ba, -N(R<sup>2</sup>)<sub>4</sub>, C<sub>1</sub>-C<sub>12</sub>-alkyl, C<sub>2</sub>-C<sub>12</sub>-alkenyl, or -R<sup>6</sup>; wherein 1 to 4 -CH<sub>2</sub> radicals of the alkyl or alkenyl group, other than the -CH<sub>2</sub> that is bound to Z, is optionally replaced by a heteroatom group selected from O, S, S(O), S(O<sub>2</sub>), or N(R<sup>2</sup>); and wherein any hydrogen in said 30 alkyl, alkenyl or R<sup>6</sup> is optionally replaced with a substituent selected from oxo, -OR<sup>2</sup>, -R<sup>2</sup>, N(R<sup>2</sup>)<sub>2</sub>, N(R<sup>2</sup>)<sub>3</sub>, R<sup>2</sup>-OH, -CN, -CO<sub>2</sub>R<sup>2</sup>, -C(O)-N(R<sup>2</sup>)<sub>2</sub>, S(O)<sub>2</sub>-N(R<sup>2</sup>)<sub>2</sub>, N(R<sup>2</sup>)-C(O)-R<sub>2</sub>, C(O)R<sup>2</sup>, -S(O)<sub>n</sub>-R<sup>2</sup>, OCF<sub>3</sub>, -S(O)<sub>n</sub>-R<sup>6</sup>, N(R<sup>2</sup>)-S(O)<sub>2</sub>(R<sup>2</sup>), halo, -CF<sub>3</sub>, or -NO<sub>2</sub>;

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M' is H, C<sub>1</sub>-C<sub>12</sub>-alkyl, C<sub>2</sub>-C<sub>12</sub>-alkenyl, or -R<sup>6</sup>;  
wherein 1 to 4 -CH<sub>2</sub> radicals of the alkyl or alkenyl group  
is optionally replaced by a heteroatom group selected from  
O, S, S(O), S(O<sub>2</sub>), or N(R<sup>2</sup>); and wherein any hydrogen in  
5 said alkyl, alkenyl or R<sup>6</sup> is optionally replaced with a  
substituent selected from oxo, -OR<sup>2</sup>, -R<sup>2</sup>, -N(R<sup>2</sup>)<sub>2</sub>, N(R<sup>2</sup>)<sub>3</sub>,  
-R<sup>2</sup>OH, -CN, -CO<sub>2</sub>R<sup>2</sup>, -C(O)-N(R<sup>2</sup>)<sub>2</sub>, -S(O)<sub>2</sub>-N(R<sup>2</sup>)<sub>2</sub>,  
-N(R<sup>2</sup>)-C(O)-R<sub>2</sub>, -C(O)R<sup>2</sup>, -S(O)<sub>n</sub>-R<sup>2</sup>, -OCF<sub>3</sub>, -S(O)<sub>n</sub>-R<sup>6</sup>,  
-N(R<sup>2</sup>)-S(O)<sub>2</sub>(R<sup>2</sup>), halo, -CF<sub>3</sub>, or -NO<sub>2</sub>;

10 Z is O, S, N(R<sup>2</sup>)<sub>2</sub>, or, when M is not present, H.  
Y is P or S;  
X is O or S; and  
R<sup>9</sup> is C(R<sup>2</sup>)<sub>2</sub>, O or N(R<sup>2</sup>); and wherein when Y is S,  
Z is not S; and

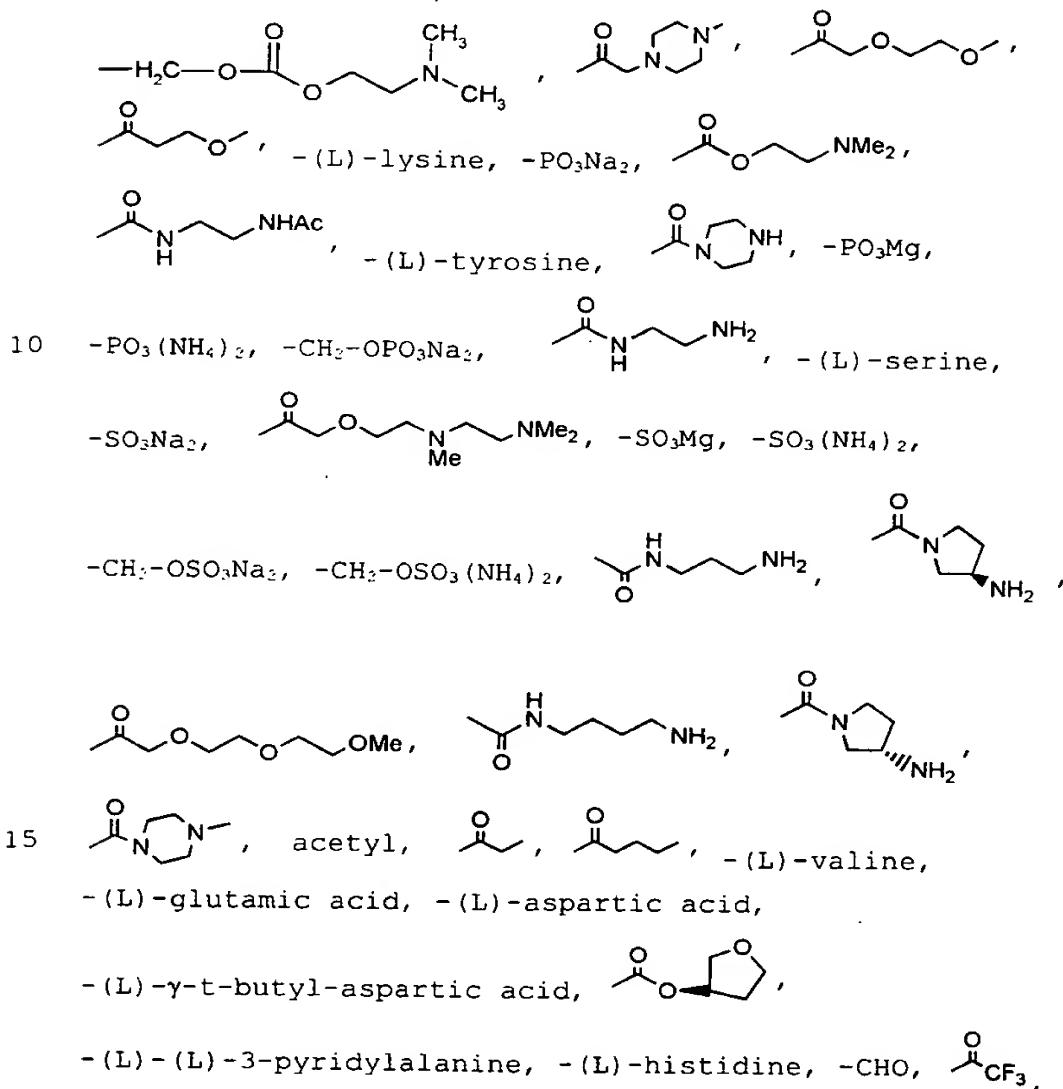
15 R<sup>6</sup> is a 5-6 membered saturated, partially  
saturated or unsaturated carbocyclic or heterocyclic ring  
system, or an 8-10 membered saturated, partially saturated  
or unsaturated bicyclic ring system; wherein any of said  
heterocyclic ring systems contains one or more heteroatoms  
20 selected from O, N, S, S(O)<sub>n</sub> or N(R<sup>2</sup>); and wherein any of  
said ring systems optionally contains 1 to 4 substituents  
independently selected from OH, C<sub>1</sub>-C<sub>4</sub> alkyl, -O-C<sub>1</sub>-C<sub>4</sub> alkyl  
or -O-C(O)-C<sub>1</sub>-C<sub>4</sub> alkyl;

25 R<sup>10</sup> is selected from C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>6</sub>-C<sub>14</sub>  
aryl or Ht, wherein R<sup>10</sup> optionally contains up to three  
substituents independently selected from -R<sup>3</sup>, -CN, -SR<sup>5</sup>,  
-SOR<sup>5</sup>, -SO<sub>2</sub>R<sup>5</sup>, -SR-NR<sup>5</sup>-C(O)R<sup>6</sup>, -NR<sup>5</sup>-(SO<sub>2</sub>)R<sup>5</sup>, -C(O)N(R<sup>5</sup>)<sub>2</sub>,  
-C(S)N(R<sup>5</sup>)<sub>2</sub>, -S(O)<sub>2</sub>N(R<sup>5</sup>)<sub>2</sub>, -C(O)R<sup>6</sup>, -C(S)R<sup>6</sup>, -N(R<sup>5</sup>)<sub>2</sub>, -NR<sup>5</sup>-  
C(O)R<sup>5</sup>, -NR<sup>5</sup>-C(O)OR<sup>5</sup>, -NR<sup>5</sup>-C(O)N(R<sup>5</sup>)<sub>2</sub>, -NR<sup>5</sup>-C(S)R<sup>5</sup>, -NR<sup>5</sup>-  
C(S)OR<sup>5</sup>, -NR<sup>5</sup>-C(S)N(R<sup>5</sup>)<sub>2</sub>, -NR<sup>5</sup>-C[=N(R<sup>5</sup>)]-N(R<sup>5</sup>)<sub>2</sub>, -NH-C[=N-NO<sub>2</sub>]-  
30 NH<sub>2</sub>, -NH-C[=N-NO<sub>2</sub>]-OR<sup>5</sup>, -N(R<sup>6</sup>)<sub>2</sub>-C(O)R<sup>6</sup>, -OC(O)R<sup>6</sup>,  
-OC(O)N(R<sup>5</sup>)<sub>2</sub>, -OC(S)N(R<sup>5</sup>)<sub>2</sub>, wherein any one of the -CH<sub>2</sub>  
groups of said alkyl or alkenyl chains of R<sup>10</sup> may be  
optionally replaced by O, S, SO, SO<sub>2</sub>, C(O) or NR<sup>5</sup>;

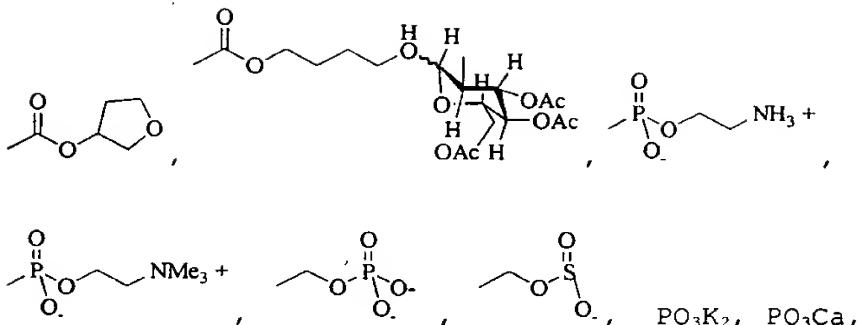
- 16 -

wherein each  $R^5$  is independently selected from hydrogen,  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl or  $Ht$ , wherein each  $R^5$ , except for hydrogen, is optionally substituted with  $-CF_3$ ,  $-PO_3R^3$ , azido or halo;

5 Preferably, at least one  $R^5$  is selected from:



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5  $\text{PO}_3$ -spermine,  $\text{PO}_3$ -(spermidine)<sub>2</sub> or  $\text{PO}_3$ -(meglamine)<sub>2</sub>.

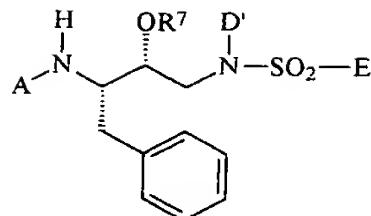
It will be understood by those of skill in the art that component M or M' in the formulae set forth herein will have either a covalent, a covalent/ zwitterionic, or an 10 ionic association with either Z or R<sup>9</sup> depending upon the actual choice for M or M'. When M or M' is hydrogen, alkyl, alkenyl, or R<sup>6</sup>, M or M' is covalently bound to R<sup>9</sup> or Z. If M is a mono- or bivalent metal or other charged species (i.e., NH<sub>4</sub><sup>+</sup>), there is an ionic interaction between M and Z 15 and the resulting compound is a salt.

When x is 0 in (M)<sub>x</sub>, Z may be a charged species. When that occurs, the other M may be oppositely charged to produce a 0 net charge on the molecule. Alternatively, the counter ion may located elsewhere in the molecule.

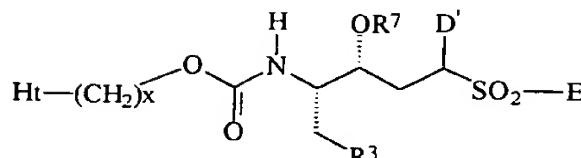
20 Except where expressly provided to the contrary, as used herein, the definitions of variables A, R<sup>1</sup>-R<sup>4</sup>, R<sup>6</sup>-R<sup>9</sup>, Ht, B, x, n, D, D', M, Q, X, Y, Z and E are to be taken as they are defined above for the compounds of formula I.

According to a preferred embodiment, the compounds 25 of this invention are those represented by formula II, formula III or formula IV:

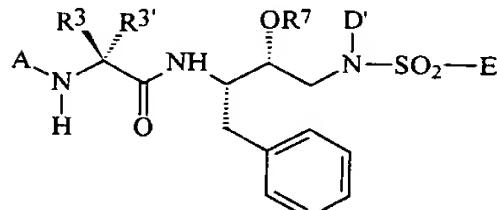
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(III)



(III)



5

(IV)

wherein A, R<sup>3</sup>, R<sup>7</sup>, Ht, D, D', x, E are as defined above for compounds of formula I. For ease of reference, the two R<sup>3</sup> moieties present in formula IV have been labeled R<sup>3</sup> and R<sup>3'</sup>.

10

For compounds of formula II, more preferred compounds are those wherein:

A is -C(O)Ht;

D' is -O-R<sup>10</sup>;

E is C<sub>6</sub>-C<sub>10</sub> aryl optionally substituted with one or more substituents selected from oxo, -OR<sup>2</sup>, SR<sup>2</sup>, -R<sup>2</sup>, -N(R<sup>2</sup>)<sub>2</sub>, -R<sup>2</sup>-OH, -CN, -CO<sub>2</sub>R<sup>2</sup>, -C(O)-N(R<sup>2</sup>)<sub>2</sub>, -S(O)<sub>2</sub>-N(R<sup>2</sup>)<sub>2</sub>, -N(R<sup>2</sup>)-C(O)-R<sup>2</sup>, -C(O)-R<sup>2</sup>, -S(O)<sub>n</sub>-R<sup>2</sup>, -OCF<sub>3</sub>, -S(O)<sub>n</sub>-Q, methylenedioxy, -N(R<sup>2</sup>)-S(O)<sub>2</sub>(R<sup>2</sup>), halo, -CF<sub>3</sub>, -NO<sub>2</sub>, Q, -OQ, -OR<sup>7</sup>, -SR<sup>7</sup>, -R<sup>7</sup>, -N(R<sup>2</sup>)(R<sup>7</sup>) or -N(R<sup>7</sup>)<sub>2</sub>; or a 5-membered heterocyclic ring containing one S and optionally containing N as an

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additional heteroatom, wherein said heterocyclic ring is optionally substituted with one to two groups independently selected from -CH<sub>3</sub>, R<sup>4</sup>, or Ht.

all other variables are as defined for formula I.

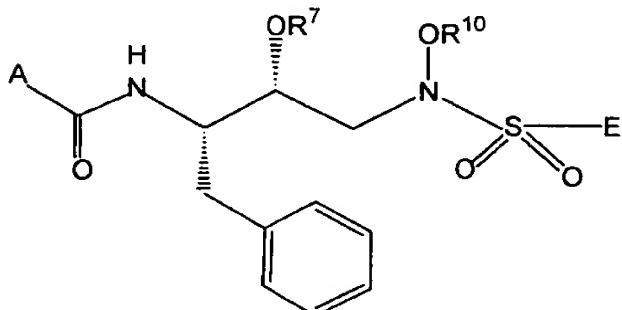
5 Another preferred embodiment for the formula II compounds are those wherein:

E is a 5-membered heterocyclic ring containing one S and optionally containing N as an additional heteroatom, wherein said heterocyclic ring is optionally substituted 10 with one to two groups independently selected from -CH<sub>3</sub>, R<sup>4</sup>, or Ht; and

all other variables are as defined for formula I.

More preferred are any of the formula II compounds set forth above, wherein R<sup>7</sup> in -OR<sup>7</sup> is -PO(OM)<sub>2</sub> or 15 C(O)CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> and both R<sup>7</sup> in -N(R<sup>7</sup>)<sub>2</sub> are H, wherein M is H, Li, Na, K or C<sub>1</sub>-C<sub>4</sub> alkyl; or wherein R<sup>7</sup> in -OR<sup>7</sup> is C(O)CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, one R<sup>7</sup> in -N(R<sup>7</sup>)<sub>2</sub> is C(O)CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> and the other is H.

20 According to another preferred embodiment of the present invention, there is provided compounds of formula (V) :



25

wherein:

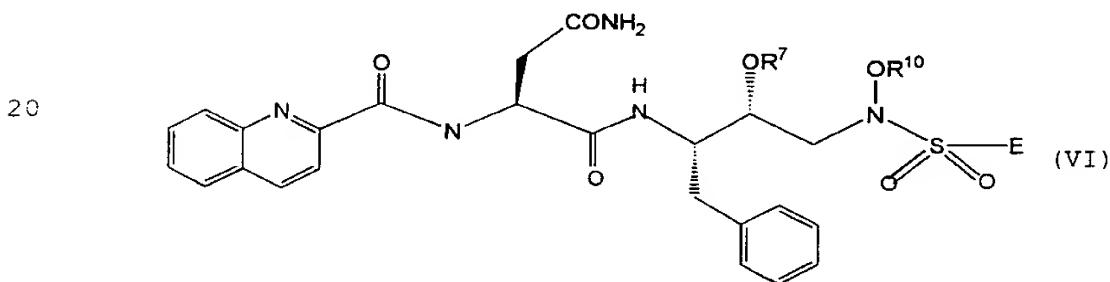
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A is  $C_6$ - $C_{14}$  aryl optionally substituted with one or more groups independently selected from the group consisting of  $C_1$ - $C_6$  alkyl or hydroxy, or  $OR^4$ , wherein  $R^4$  is  $C_1$ - $C_8$  alkyl,  $C_3$ - $C_7$  cycloalkyl,  $C_1$ - $C_8$  alkyl substituted with  $C_6$ - $C_{14}$ ,  $C_6$ - $C_{14}$  5 aryl optionally substituted with  $C_1$ - $C_8$  alkyl, heterocyclyl or heterocyclylalkyl;

E is  $C_6$ - $C_{14}$  aryl, optionally substituted with one or more groups selected from nitro, oxo, alkoxy, amino, hydroxyamino; heterocyclyl, optionally substituted with one 10 or more groups selected from the group consisting of nitro, oxo, alkoxy, amino, hydroxyamino or  $N(CO)OCH_3$ ;

$R^{10}$  and  $R^7$  are as defined above;  
or a pharmaceutically acceptable derivative thereof.

15 According to yet another preferred embodiment, there is provided compounds of Formula (VI):



25 wherein:

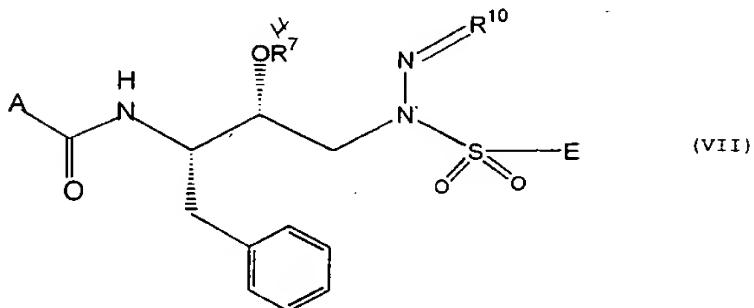
$R^7$  and  $R^{10}$  are as defined above for formula I;

E is  $C_6$ - $C_{14}$  aryl, optionally substituted with one or more groups selected from the group consisting of nitro, oxo, alkoxy, amino, hydroxyamino; heterocyclyl, optionally substituted with one or more groups selected from the group consisting of nitro, oxo, alkoxy, amino, hydroxyamino or  $N(CO)OCH_3$ ;

30 or a pharmaceutically acceptable derivative thereof.

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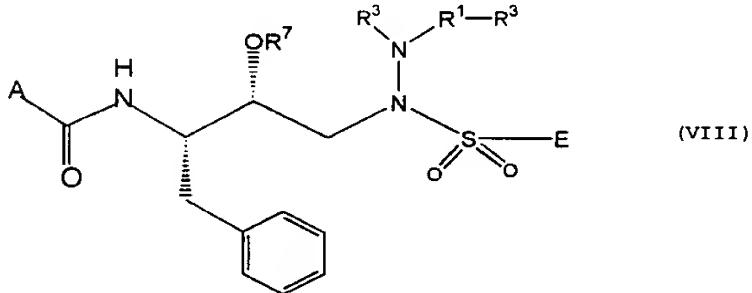
According to yet another preferred embodiment, there is provided a compound of Formula (VII):



5 wherein:

$\text{A}$ ,  $\text{E}$ ,  $\text{R}^7$  and  $\text{R}^{10}$  are as defined in formula (I); or a pharmaceutically acceptable derivative thereof.

10 According to yet another preferred embodiment, there is provided a compound of formula (VIII):



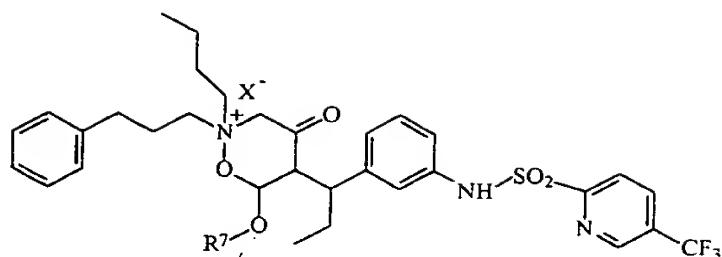
wherein  $\text{A}$ ,  $\text{R}^1$ ,  $\text{R}^3$ ,  $\text{R}^7$  and  $\text{E}$  are as defined in formula (I).

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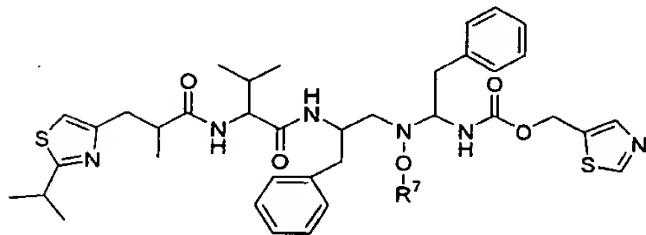
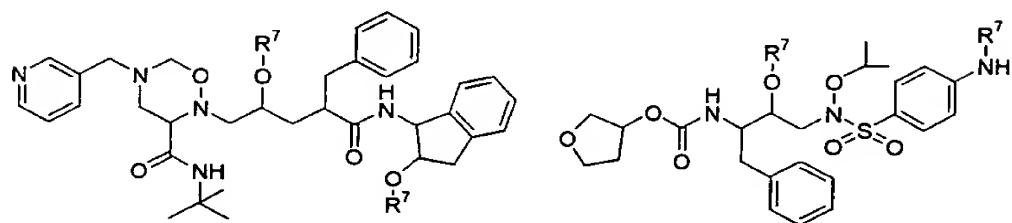
According to yet another embodiment of the present invention, there are provided compounds of the formula:

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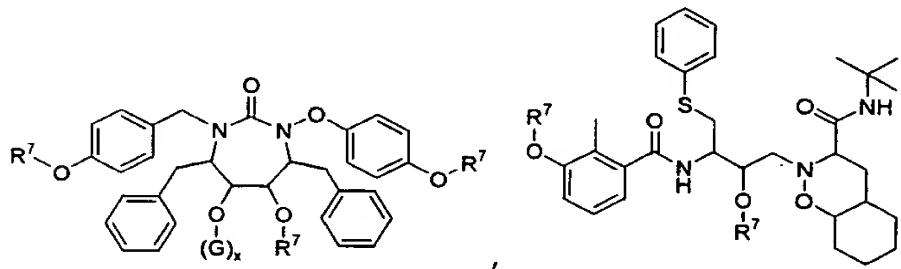
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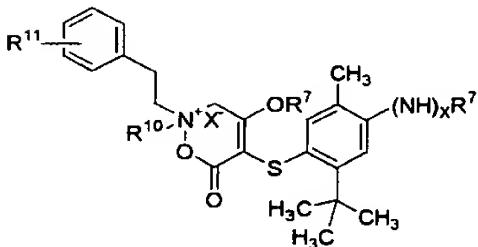
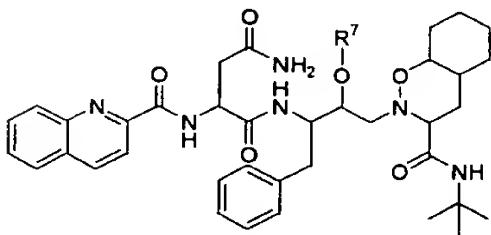
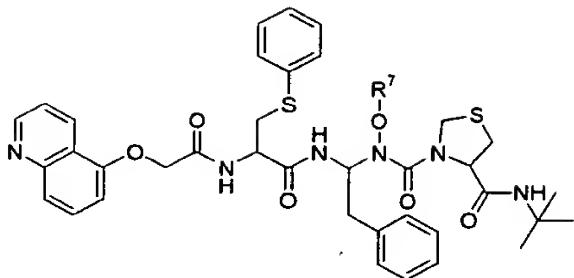


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wherein  $R^{10}$  is selected from isopropyl or cyclopentyl;  $R^{11}$  is selected from  $NHR^7$  or  $OR^7$ ;  $x$ ,  $R^7$  and  $G$  are as defined above; and  $X^-$  is a pharmaceutically acceptable counterion.

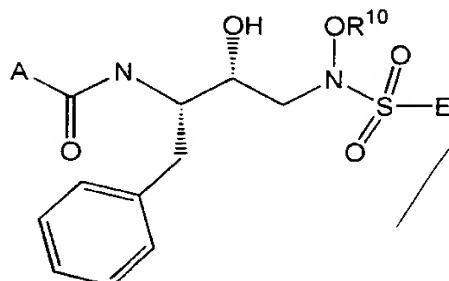
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The compounds according to the invention contain one or more asymmetric carbon atoms and thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be of the R or S configuration. Although the specific compounds exemplified in this application may be depicted in a particular stereochemical configuration, compounds having

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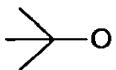
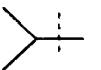
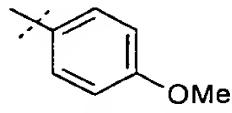
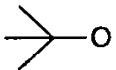
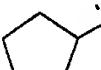
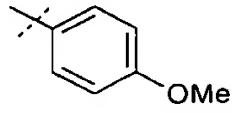
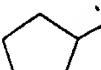
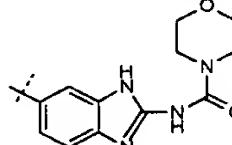
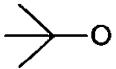
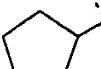
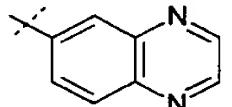
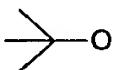
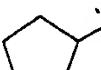
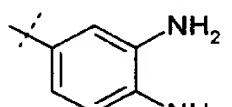
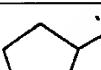
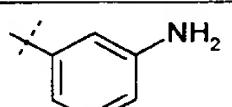
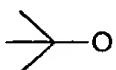
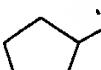
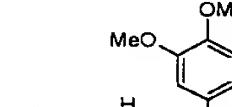
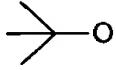
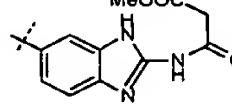
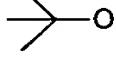
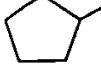
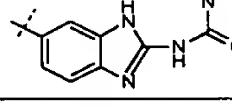
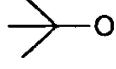
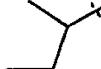
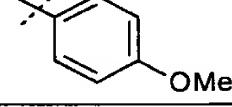
either the opposite stereochemistry at any given chiral center or mixtures thereof are also envisioned.

More preferred compounds of formula (I) of the  
5 present invention are set forth below in Table 1.

Table 1

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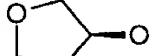
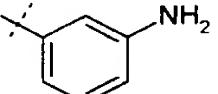
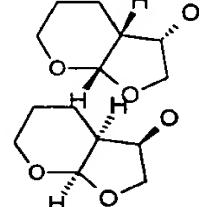
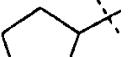
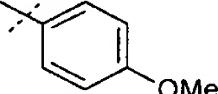
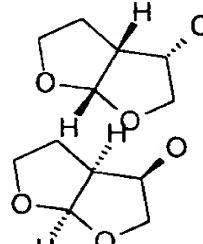
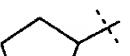
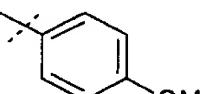
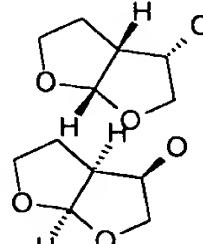
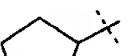
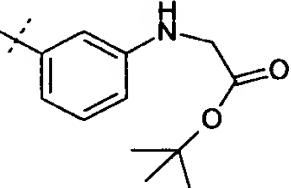
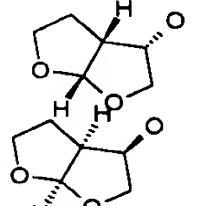
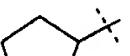
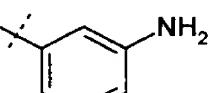
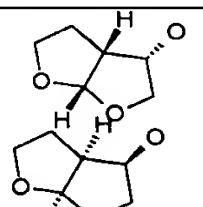
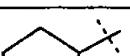
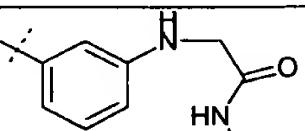
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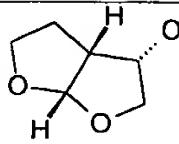
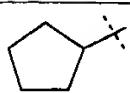
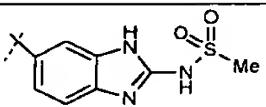
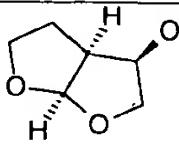
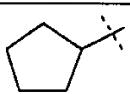
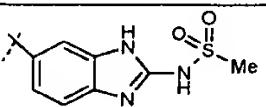
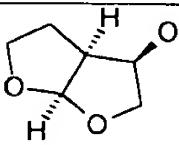
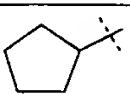
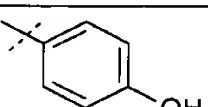
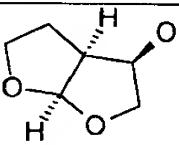
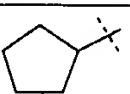
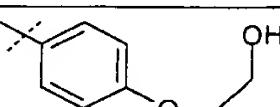
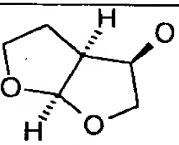
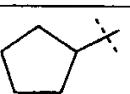
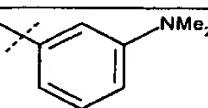
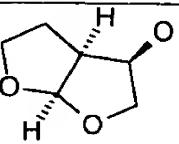
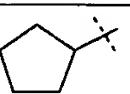
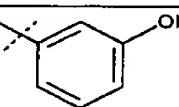
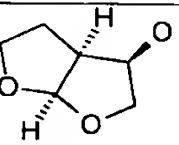
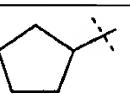
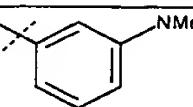
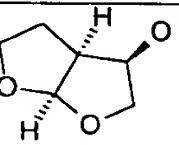
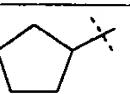
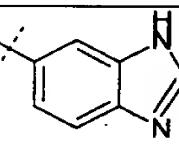
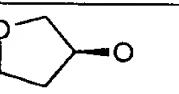
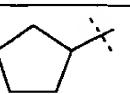
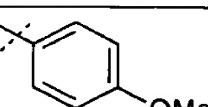
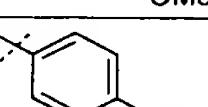
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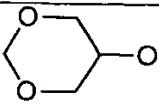
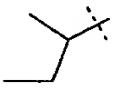
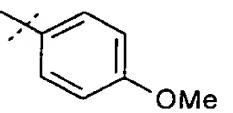
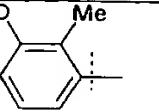
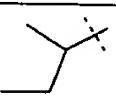
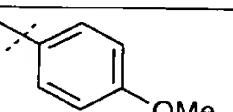
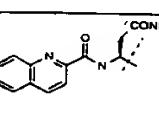
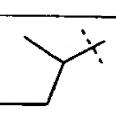
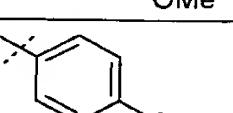
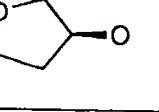
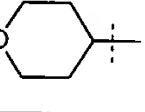
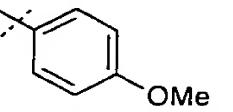
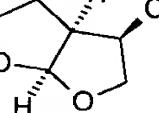
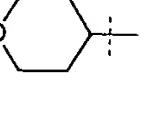
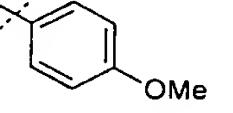
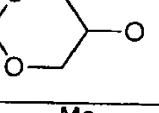
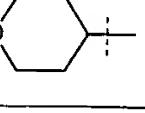
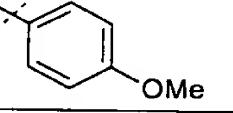
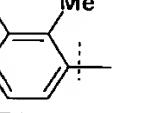
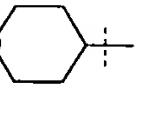
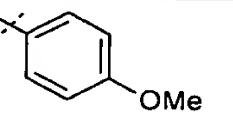
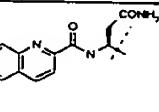
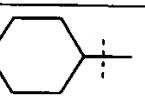
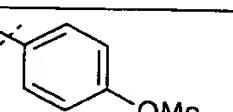
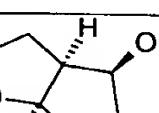
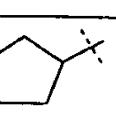
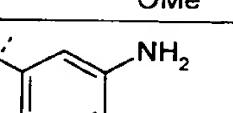
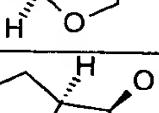
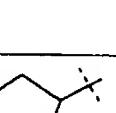
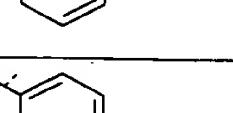
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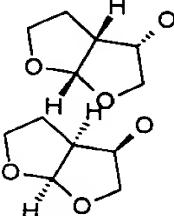
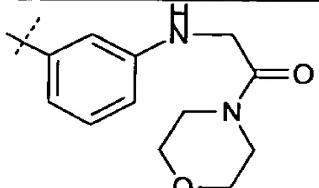
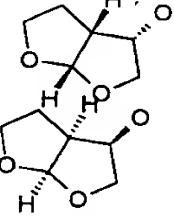
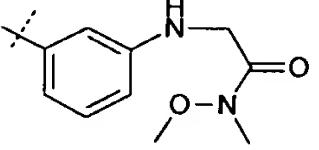
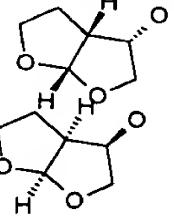
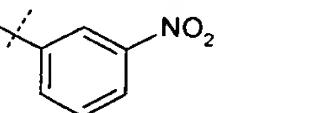
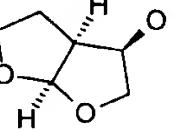
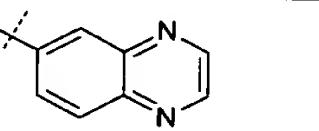
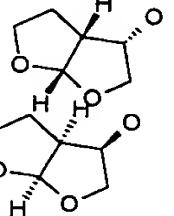
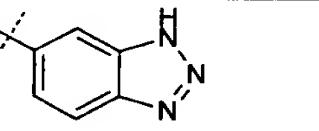
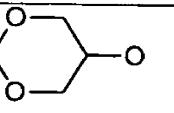
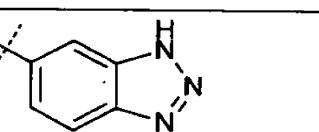
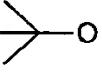
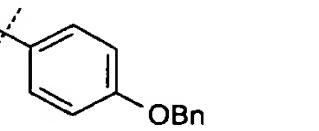
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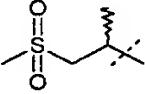
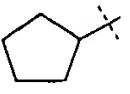
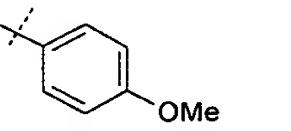
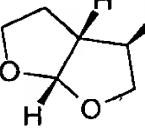
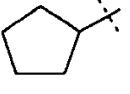
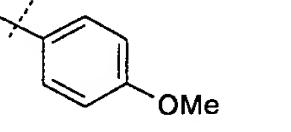
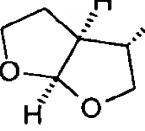
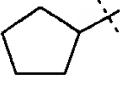
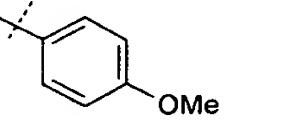
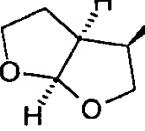
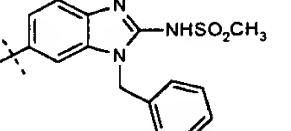
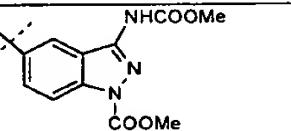
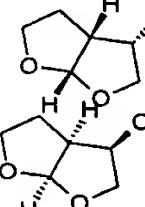
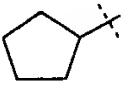
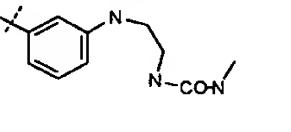
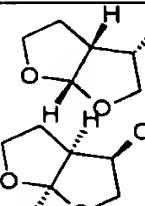
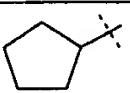
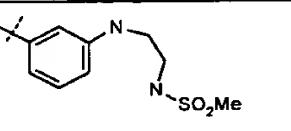
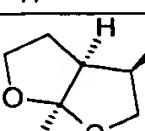
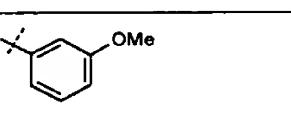
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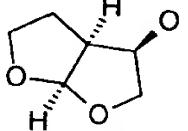
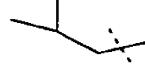
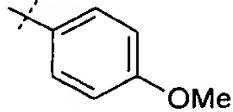
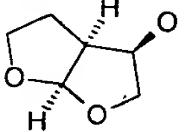
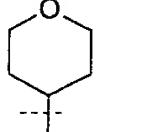
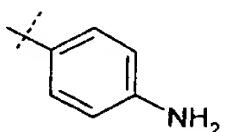
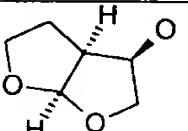
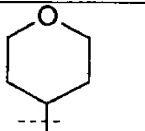
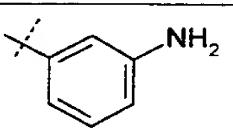
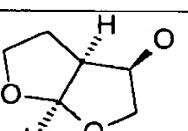
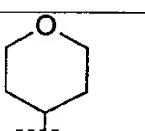
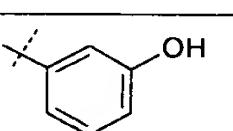
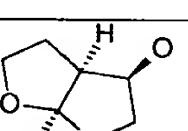
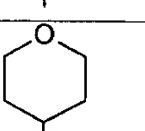
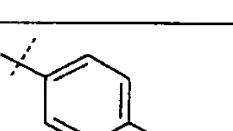
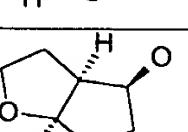
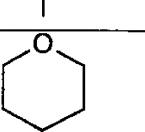
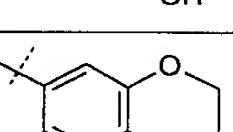
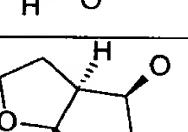
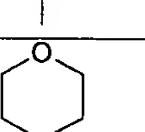
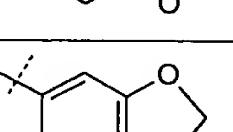
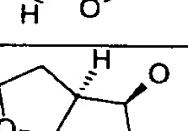
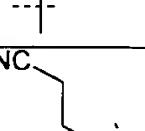
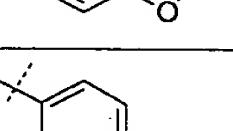
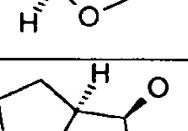
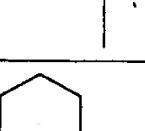
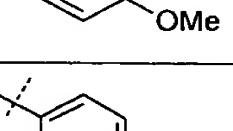
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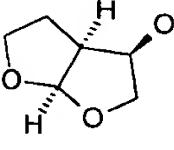
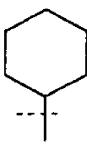
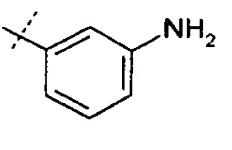
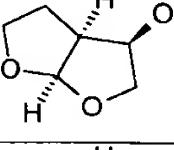
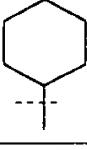
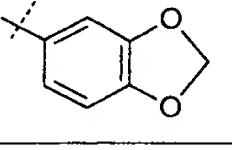
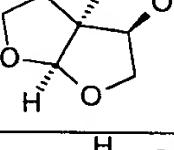
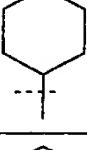
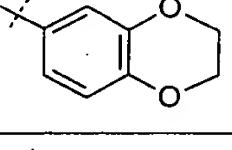
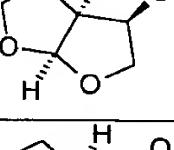
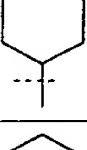
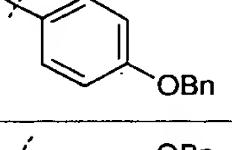
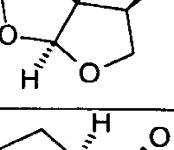
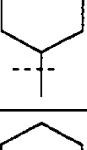
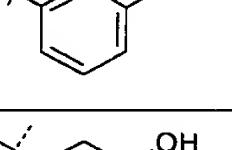
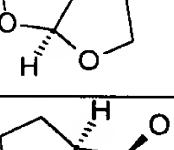
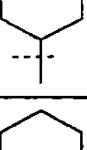
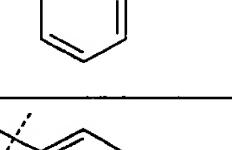
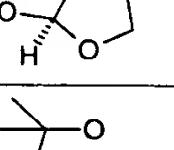
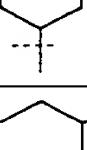
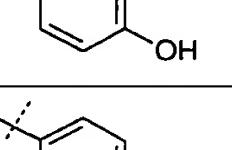
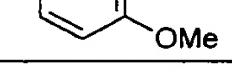
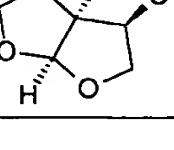
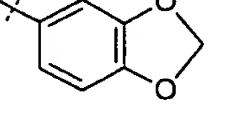
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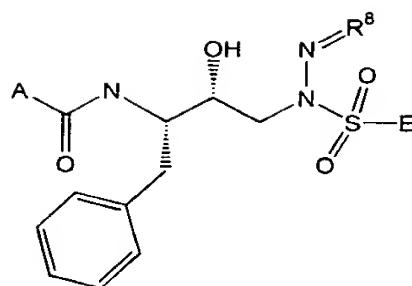
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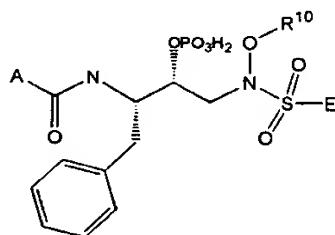
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5

Compound	A	R <sup>8</sup>	E
80			
81			



10

Compound	A	R <sup>10</sup>	E
100			

101			
119			
143			
144			

Most preferred compounds of the present invention include the following:

5 (3*R*, 3*aS*, 6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*, 2*R*)-1-benzyl-3-(cyclopentyloxy){(3-[2-(dimethylamino)ethyl]aminophenyl)sulfonyl]amino-2-hydroxypropyl)carbamate;

(3*S*, 3*aR*, 6*aS*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*, 2*R*)-1-benzyl-3-(cyclopentyloxy){(3-[2-(dimethylamino)ethyl]aminophenyl)sulfonyl]amino-2-hydroxypropyl)carbamate;

10 (3*R*, 3*aS*, 6*aR*)Hexahydrofuro[2,3-*b*]furan-3-yl-*N*-((1*S*, 2*R*)-1-benzyl-3-(cyclopentyloxy)(2-[(methylsulfonyl)amino]benzimidazol-5-ylsulfonyl)amino-2-hydroxypropyl)carbamate;

(3*R*, 3*aS*, 6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*, 2*R*)-3-[(3-N-methylaminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate;

1,3-Dioxan-5-yl N-(1*S*,2*R*)-1-benzyl-3-[(cyclopentyloxy)  
(2-[(methoxycarbonyl)amino]-1*H*-benzimidazol-5-ylsulfonyl)  
amino]-2-hydroxypropylcarbamate;

5 (3*R*,3*aS*,6*aR*) hexahydrofuro[2,3-*b*]furan-3-yl N-(1*S*,2*R*)-1-  
benzyl-2-hydroxy-3-[(4-methoxyphenyl)sulfonyl](tetrahydro-  
2*H*-pyran-4-yl)oxy)amino]propylcarbamate;

(3*R*,3*aS*,6*aR*) hexahydrofuro[2,3-*b*]furan-3-yl N-(1*S*,2*R*)-3-  
[(3-aminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-  
hydroxypropylcarbamate;

10 (3*R*,3*aS*,6*aR*) hexahydrofuro[2,3-*b*]furan-3-yl N-[(1*S*,2*R*)-  
1-benzyl-3-[(cyclopentyloxy)[3-(2-[methoxy(methyl)amino]-2-  
oxoethylamino)phenyl]sulfonylamino]-2-hydroxypropyl]  
carbamate;

15 (3*R*,3*aS*,6*aR*) hexahydrofuro[2,3-*b*]furan-3-yl N-[(1*S*,2*R*)-  
1-benzyl-4-(cyclopentyloxy)-2-hydroxy-4-(6-quinoxalinyl  
sulfonyl)butyl] carbamate;

(3*R*,3*aS*,6*aR*) hexahydrofuro[2,3-*b*]furan-3-yl N-[(1*S*,2*R*)-  
1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-  
2-hydroxypropyl]carbamate;

20 (3*R*,3*aS*,6*aR*) hexahydrofuro[2,3-*b*]furan-3-yl N-[(1*S*,2*R*)-  
1-benzyl-3-[(cyclopentyloxy)[3-(2-[(methylsulfonyl)amino]  
ethylamino)phenyl]sulfonylamino]-2-hydroxypropyl]carbamate;

25 (3*R*,3*aS*,6*aR*) hexahydrofuro[2,3-*b*]furan-3-yl N-(1*S*,2*R*)-3-  
[(3-N-methylaminophenyl)sulfonyl](cyclopentyloxy)amino]-1-  
benzyl-2-hydroxypropylcarbamate phosphate ester;

(3*R*,3*aS*,6*aR*) hexahydrofuro[2,3-*b*]furan-3-yl N-(1*S*,2*R*)-3-  
[(3-aminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-  
hydroxypropylcarbamate phosphate ester;

30 (3*R*,3*aS*,6*aR*) hexahydrofuro[2,3-*b*]furan-3-yl N-(1*S*,2*R*)-3-  
[(4-aminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-  
2-hydroxypropyl carbamate;

(3*R*,3*aS*,6*aR*) hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-  
benzyl-3-[(1-ethylpropoxy)[(4-hydroxyphenyl)sulfonyl]amino]-  
2-hydroxypropylcarbamate;

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(3R, 3aS, 6aR)hexahydrofuro[2, 3-b]furan-3-yl (1S, 2R)-3-[(1, 3-benzodioxol-5-ylsulfonyl) (1-ethylpropoxy) amino]-1-benzyl-2-hydroxypropylcarbamate;

5 (3R, 3aS, 6aR)hexahydrofuro[2, 3-b]furan-3-yl N-[(1S, 2R)-3-[(1, 3-benzodioxol-5-ylsulfonyl) (cyclopentyloxy) amino]-1-benzyl-2-(phosphonoxy) propyl]carbamate;

(3R, 3aS, 6aR)hexahydrofuro[2, 3-b]furan-3-yl (1S, 2R)-3-[(1, 3-benzodioxol-5-ylsulfonyl) (cyclohexyloxy) amino]-1-benzyl-2-hydroxypropylcarbamate;

10 (3R, 3aS, 6aR)hexahydrofuro[2, 3-b]furan-3-yl 3-[(1, 3-benzodioxol-5-ylsulfonyl) (tetrahydro-2H-pyran-4-yloxy) amino]-1-benzyl-2-hydroxypropylcarbamate;

15 (3R, 3aS, 6aR)hexahydrofuro[2, 3-b]furan-3-yl N-[(1S, 2R)-3-[(1, 3-benzodioxol-5-ylsulfonyl) (cyclopentyloxy) amino]-1-benzyl-2-(phosphonoxy) propyl]carbamate;

or a pharmaceutically acceptable derivative thereof.

The compounds of the present invention can be readily prepared by techniques known in the art. Scheme I 20 illustrates a general synthetic route to compounds of formula (V), a preferred sub-genus of formula (I).

According to Scheme I, commercially available N-hydroxyphthalimide is reacted with R<sup>10</sup>-Br or R<sup>10</sup>-OH under displacement or Mitsonobu-type conditions respectively, 25 followed by hydrazinolysis in ethanol to produce the amine of formula (I). Amine of formula (I) is further utilized in two synthetic routes, Path 1 and Path 2.

Path 1

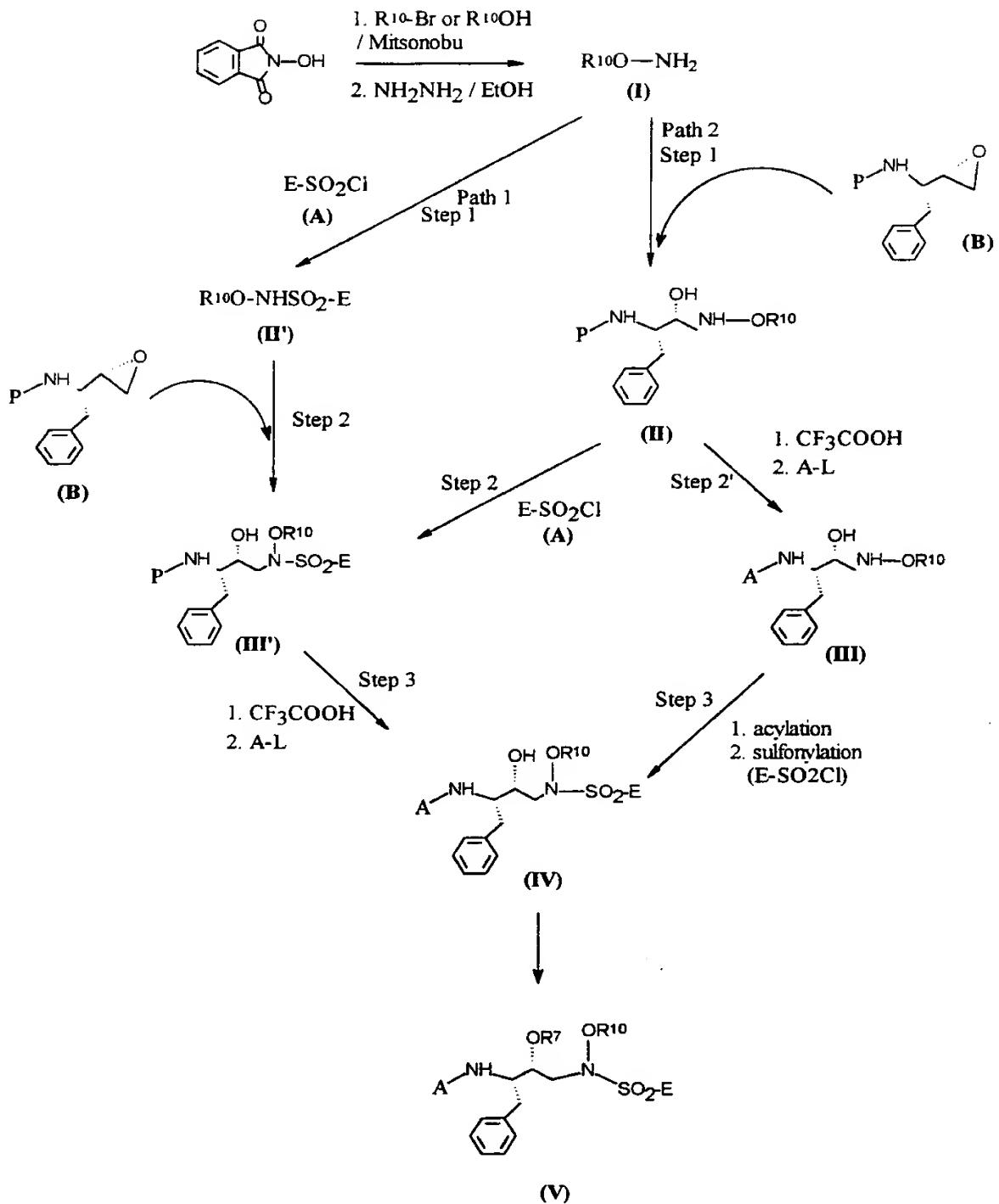
30 Step 1: Amine of formula (I) is reacted with a sulfonyl chloride of formula (A) to produce sulfonamide of formula (II').

Step 2: Sulfonamide of formula (II') is reacted with intermediate of formula (B), which bears an amine protecting

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group P, such as t-butoxycarbonyl, to produce compound of formula (III'). Suitable amine protecting groups are described in numerous references, including T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 2d 5 Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic Synthesis, John Wiley and Sons (1994); and L. Paquette, ed. Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995). Examples of such amino protecting groups include, but are 10 not limited to, Cbz or Alloc.

Step 3: Compound of formula (III') is then reacted with A-L, wherein L is a leaving group, to produce compound of formula (IV). A leaving group is an atom or group which is displaceable upon reaction with an appropriate amine or 15 sulfonamide. Suitable leaving groups would be obvious to one of skill in the art and include but are not limited to hydroxyls, carboxylates and halides.

**SCHEME I**

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Step 4: Compound of formula (IV) is then converted to compound of formula (V) by functional transformation of the hydroxy group.

5 Path 2 differs from Path 1 only in the sequence of reagents employed to convert compound of formula (I) to compound of formula (IV).

10 The synthetic approach illustrated in Scheme I can be readily extended to produce other compounds of the present invention. The above synthetic scheme is not intended to comprise a comprehensive list of all means by which compounds described and claimed in this application may be synthesized. Further methods will be evident to 15 those of ordinary skill in the art.

As discussed above, the novel compounds of the present invention are excellent ligands for aspartyl proteases, particularly HIV-1 and HIV-2 proteases.

Accordingly, these compounds are capable of targeting and 20 inhibiting late stage events in HIV replication, i.e., the processing of the viral polyproteins by HIV encoded proteases. Such compounds inhibit the proteolytic processing of viral polyprotein precursors by inhibiting aspartyl protease. Because aspartyl protease is essential 25 for the production of mature virions, inhibition of that processing effectively blocks the spread of virus by inhibiting the production of infectious virions, particularly from chronically infected cells. Compounds according to this invention advantageously inhibit the 30 ability of the HIV-1 virus to infect immortalized human T cells over a period of days, as determined by an assay of extracellular p24 antigen -- a specific marker of viral replication. Other anti-viral assays have confirmed the potency of these compounds.

The compounds of this invention may be employed in a conventional manner for the treatment of viruses, such as HIV and HTLV, which depend on aspartyl proteases for obligatory events in their life cycle. Such methods of 5 treatment, their dosage levels and requirements may be selected by those of ordinary skill in the art from available methods and techniques. For example, a compound of this invention may be combined with a pharmaceutically acceptable adjuvant for administration to a virally-infected 10 patient in a pharmaceutically acceptable manner and in an amount effective to lessen the severity of the viral infection.

Alternatively, the compounds of this invention may be used in vaccines and methods for protecting individuals 15 against viral infection over an extended period of time. The compounds may be employed in such vaccines either alone or together with other compounds of this invention in a manner consistent with the conventional utilization of protease inhibitors in vaccines. For example, a compound of 20 this invention may be combined with pharmaceutically acceptable adjuvants conventionally employed in vaccines and administered in prophylactically effective amounts to protect individuals over an extended period time against HIV infection. As such, the novel protease inhibitors of this 25 invention can be administered as agents for treating or preventing HIV infection in a mammal.

The compounds of formula I, especially those having a molecular weight of less than about 700 g/mole, may be readily absorbed by the bloodstream of mammals upon oral 30 administration. Compounds of formula I having a molecular weight of less than about 600 g/mole are most likely to demonstrate oral availability. This surprisingly impressive oral availability makes such compounds excellent agents for

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orally-administered treatment and prevention regimens against HIV infection.

The compounds of this invention may be administered to a healthy or HIV-infected patient either as a single agent or in combination with other anti-viral agents which interfere with the replication cycle of HIV. By administering the compounds of this invention with other anti-viral agents which target different events in the viral life cycle, the therapeutic effect of these compounds is potentiated. For instance, the co-administered anti-viral agent can be one which targets early events in the life cycle of the virus, such as cell entry, reverse transcription and viral DNA integration into cellular DNA. Anti-HIV agents targeting such early life cycle events include, didanosine (ddI), alcitabine (ddC), d4T, zidovudine (AZT), polysulfated polysaccharides, ST4 (soluble CD4), 3TC, 935U83, 1592U89, 524W91, ganciclovir, dideoxycytidine, trisodium phosphonoformate, eflornithine, ribavirin, acyclovir, alpha interferon and trimenotrexate.

Ribonucleotide reductase inhibitors such as hydroxyurea may also be used. Additionally, non-nucleoside inhibitors of reverse transcriptase, such as TIBO, delavirine (U90) or nevirapine, may be used to potentiate the effect of the compounds of this invention, as may viral uncoating inhibitors, inhibitors of trans-activating proteins such as tat or rev, or inhibitors of the viral integrase.

Combination therapies according to this invention exert a synergistic effect in inhibiting HIV replication because each component agent of the combination acts on a different site of HIV replication. The use of such combinations also advantageously reduces the dosage of a given conventional anti-retroviral agent which would be required for a desired therapeutic or prophylactic effect as compared to when that agent is administered as a

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monotherapy. These combinations may reduce or eliminate the side effects of conventional single anti-retroviral agent therapies while not interfering with the anti-retroviral activity of those agents. These combinations reduce 5 potential of resistance to single agent therapies, while minimizing any associated toxicity. These combinations may also increase the efficacy of the conventional agent without increasing the associated toxicity. In particular, we have discovered that these compounds act synergistically in 10 preventing the replication of HIV in human T cells.

Preferred combination therapies include the administration of a compound of this invention with AZT, ddI, ddC or d4T.

Alternatively, the compounds of this invention may also be co-administered with other HIV protease inhibitors 15 such as Agenerase (VX-478, Vertex), saquinavir, Ro 31-8959 (Roche), L-735,524 (Merck), XM 323 (Du-Pont Merck) A-80,987 (Abbott), MK 639 (Merck), ABT 538 (A-80538, Abbott), AG 1343(Agouron), XM 412 (Du-Pont Merck), XM 450 (Du-Pont Merck), BMS 186318 (Bristol-Meyers Squibb), ABT 378 (Abbott) 20 and CPG 53,437 (Ciba Geigy) to increase the effect of therapy or prophylaxis against various viral mutants or members of other HIV quasi species.

We prefer administering the compounds of this invention as single agents or in combination with retroviral 25 reverse transcriptase inhibitors, such as derivatives of AZT, or other HIV aspartyl protease inhibitors. We believe that the co-administration of the compounds of this invention with retroviral reverse transcriptase inhibitors or HIV aspartyl protease inhibitors may exert a substantial 30 synergistic effect, thereby preventing, substantially reducing, or completely eliminating viral infectivity and its associated symptoms.

The compounds of this invention can also be administered in combination with immunomodulators (e.g.,

bropirimine, anti-human alpha interferon antibody, IL-2, GM-CSF, methionine enkephalin, interferon alpha, diethyldithiocarbamate, tumor necrosis factor, naltrexone, tuscarasol and rEPO); and antibiotics (e.g., pentamidine isethionate) to prevent or combat infection and disease associated with HIV infections, such as AIDS and ARC.

When the compounds of this invention are administered in combination therapies with other agents, they may be administered sequentially or concurrently to the patient.

10 Alternatively, pharmaceutical or prophylactic compositions according to this invention may be comprised of a combination of an aspartyl protease inhibitor of this invention and another therapeutic or prophylactic agent.

15 Although this invention focuses on the use of the compounds disclosed herein for preventing and treating HIV infection, the compounds of this invention can also be used as inhibitory agents for other viruses which depend on similar aspartyl proteases for obligatory events in their life cycle. These viruses include, as well as other AIDS-like 20 diseases caused by retroviruses, such as simian immunodeficiency viruses, but are not limited to, HTLV-I and HTLV-II. In addition, the compounds of this invention may also be used to inhibit other aspartyl proteases, and in particular, other human aspartyl proteases, including renin 25 and aspartyl proteases that process endothelin precursors. Pharmaceutical compositions of this invention comprise any of the compounds of the present invention, and pharmaceutically acceptable salts thereof, with any pharmaceutically acceptable carrier, adjuvant or vehicle.

30 Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as

phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, 5 sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and 10 wool fat.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. We prefer oral administration or 15 administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, 20 intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile 25 injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents 30 that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition,

sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride

5 derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant such as

10 Ph. Helv or a similar alcohol.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets

15 for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are

20 administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions of this invention may

25 also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in

30 the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

Topical administration of the pharmaceutical compositions of this invention is especially useful when the

desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active 5 components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax 10 and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters 15 wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches are also 20 included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared 25 as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

Dosage levels of between about 0.01 and about 100 30 mg/kg body weight per day, preferably between about 0.5 and about 50 mg/kg body weight per day of the active ingredient compound are useful in the prevention and treatment of viral infection, including HIV infection. Typically, the pharmaceutical compositions of this invention will be

administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with 5 the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Preferably, such preparations contain from about 20% to about 80% active 10 compound.

Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of 15 administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. Patients may, however, require intermittent treatment on a long-term basis 20 upon any recurrence of disease symptoms.

As the skilled artisan will appreciate, lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the 25 activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the infection, the patient's disposition to the infection and the judgment of the 30 treating physician.

The compounds of this invention are also useful as commercial reagents which effectively bind to aspartyl proteases, particularly HIV aspartyl protease. As commercial reagents, the compounds of this invention, and

their derivatives, may be used to block proteolysis of a target peptide or may be derivatized to bind to a stable resin as a tethered substrate for affinity chromatography applications. These and other uses which characterize 5 commercial aspartyl protease inhibitors will be evident to those of ordinary skill in the art.

As used herein, the compounds according to the invention are defined to include pharmaceutically acceptable derivatives or prodrugs thereof. A "pharmaceutically 10 acceptable derivative" or "pharmaceutically acceptable prodrug" means any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of this invention which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of 15 this invention or an inhibitorily active metabolite or residue thereof. Particularly favored derivatives and prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal (e.g., by allowing an orally 20 administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species.

The compounds according to the invention may be 25 used in the form of salts derived from inorganic or organic acids. Included among such acid salts, for example, are the following: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, 30 dodecylsulfate, ethanesulfonate, fumarate, flucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate,

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pectianate, persulfate, phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate and undecanoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be 5 employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g. sodium), alkaline earth metal (e.g., 10 magnesium), ammonium and  $\text{NW}_4^+$  (wherein W is  $\text{C}_{1-4}$  alkyl). Physiologically acceptable salts of a hydrogen atom or an amino group include salts of organic carboxylic acids such as acetic, lactic, tartaric, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids such as 15 methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids and inorganic acids such as hydrochloric, sulfuric, phosphoric and sulfamic acids. Physiologically acceptable salts of a compound with a hydroxy group include the anion of said compound in 20 combination with a suitable cation such as  $\text{Na}^+$ ,  $\text{NH}_4^+$ , and  $\text{NW}_4^+$  (wherein W is a  $\text{C}_{1-4}$  alkyl group).

Pharmaceutically acceptable salts include salts of organic carboxylic acids such as ascorbic, acetic, citric, lactic, tartaric, malic, maleic, isothionic, lactobionic, p-25 aminobenzoic and succinic acids; organic sulphonic acids such as methanesulphonic, ethanesulphonic, benzenesulphonic and p-toluenesulphonic acids and inorganic acids such as hydrochloric, sulphuric, phosphoric, sulphamic and pyrophosphoric acids.

30 For therapeutic use, salts of the compounds according to the invention will be pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for

example, in the preparation or purification of a pharmaceutically acceptable compound.

Preferred salts include salts formed from hydrochloric, sulfuric, acetic, succinic, citric and 5 ascorbic acids.

Preferred esters of the compounds according to the invention are independently selected from the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-10 carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxyethyl), 15 aryl (for example, phenyl optionally substituted by, for example, halogen, C<sub>1-4</sub>alkyl, or C<sub>1-4</sub>alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters 20 and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C<sub>1-20</sub> alcohol or reactive derivative thereof, or by a 2,3-di(C<sub>6-24</sub>)acyl glycerol.

In such esters, unless otherwise specified, any 25 alkyl moiety present advantageously contains from 1 to 18 carbon atoms, particularly from 1 to 6 carbon atoms, more particularly from 1 to 4 carbon atoms. Any cycloalkyl moiety present in such esters advantageously contains from 3 to 6 carbon atoms. Any aryl moiety present in such esters 30 advantageously comprises a phenyl group.

Any reference to any of the above compounds also includes a reference to a pharmaceutically acceptable salts thereof.

The compounds according to the invention are especially useful for the treatment of AIDS and related clinical conditions such as AIDS related complex (ARC), progressive generalized lymphadenopathy (PGL), Kaposi's 5 sarcoma, thrombocytopenic purpura, AIDS-related neurological conditions such as AIDS dementia complex, multiple sclerosis or tropical paraparesis, and also anti-HIV antibody-positive and HIV-positive conditions, including such conditions in asymptomatic patients.

10 In a further aspect of the invention there are provided the compounds according to the invention for use in medical therapy particularly for the treatment or prophylaxis of viral infections such as HIV infections.

15 According to another aspect, the present invention provides a method for the treatment or prevention of the symptoms or effects of a viral infection in an infected animal, for example, a mammal including a human, which comprises treating said animal with a therapeutically effective amount of a compound according to the invention.

20 According to a particular embodiment of this aspect of the invention, the viral infection is an HIV infection. A further aspect of the invention includes a method for the treatment or prevention of the symptoms or effects of an HBV infection.

25 The compounds according to the invention may also be used in adjuvant therapy in the treatment of HIV infections or HIV-associated symptoms or effects, for example Kaposi's sarcoma.

30 The present invention further provides a method for the treatment of a clinical condition in an animal, for example, a mammal including a human which clinical condition includes those which have been discussed in the introduction hereinbefore, which comprises treating said animal with a therapeutically effective amount of a compound according to

the invention. The present invention also includes a method for the treatment or prophylaxis of any of the aforementioned infections or conditions.

In yet a further aspect, the present invention 5 provides the use of a compound according to the invention in the manufacture of a medicament for the treatment or prophylaxis of any of the above mentioned viral infections or conditions. It will be appreciated that of compounds of Formula (I), (II), (III), (IV), and (V) and one or more 10 other HIV protease inhibitors, reverse transcriptase inhibitors, or non-nucleoside reverse transcriptase inhibitors may be used in the manufacture of the above medicament.

Reference herein to treatment extends to 15 prophylaxis as well as the treatment of established infections or symptoms.

The above compounds according to the invention and 20 their pharmaceutically acceptable derivatives may be employed in combination with other therapeutic agents for the treatment of the above infections or conditions.

Combination therapies according to the present invention comprise the administration of at least one compound of the formula (I) or a pharmaceutically acceptable derivative 25 thereof and at least one other pharmaceutically active ingredient. The active ingredient(s) and pharmaceutically active agents may be administered simultaneously in either the same or different pharmaceutical formulations or sequentially in any order. The amounts of the active ingredient(s) and pharmaceutically active agent(s) and the 30 relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. Preferably the combination therapy involves the administration of one compound according to the invention and one of the agents mentioned herein below.

Examples of such further therapeutic agents include agents that are effective for the treatment of viral infections or associated conditions such as (1 alpha, 2 beta, 3 alpha)-9-[2,3-bis(hydroxymethyl)cyclobutyl]guanine [(-)BHCG, SQ-34514], oxetanocin-G (3,4-bis-(hydroxymethyl)-2-oxetanosyl]guanine), acyclic nucleosides (e.g. acyclovir, valaciclovir, famciclovir, ganciclovir, penciclovir), acyclic nucleoside phosphonates (e.g. (S)-1-(3-hydroxy-2-phosphonyl-methoxypropyl)cytosine (HPMPC), ribonucleotide reductase inhibitors such as 2-acetylpyridine 5-[(2-chloroanilino)thiocarbonyl] thiocarbonohydrazone, 3'azido-3'-deoxythymidine, hydroxyurea, other 2',3'-dideoxynucleosides such as 2',3'-dideoxycytidine, 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine, 2',3'-didehydrothymidine, protease inhibitors such as agenerase, indinavir, ritonavir, nelfinavir, [3S-[3R\*(1R\*, 2S\*)]]-[3[[4-aminophenyl]sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-tetrahydro-3-furanyl ester (141W94), oxathiolane nucleoside analogues such as (-)-cis-1-(2-hydroxymethyl)-1,3-oxathiolane 5-yl)-cytosine (lamivudine) or cis-1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-5-fluorocytosine (FTC), 3'-deoxy-3'-fluorothymidine, 5-chloro-2',3'-dideoxy-3'-fluorouridine, (-)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol, ribavirin, 9-[4-hydroxy-2-(hydroxymethyl)but-1-yl]-guanine (H2G), tat inhibitors such as 7-chloro-5-(2-pyrryl)-3H-1,4-benzodiazepin-2-(H)one (Ro5-3335), 7-chloro-1,3-dihydro-5-(1H-pyrrol-2-yl)-3H-1,4-benzodiazepin-2-amine (Ro24-7429), interferons such as  $\alpha$ -interferon, renal excretion inhibitors such as probenecid, nucleoside transport inhibitors such as dipyridamole; pentoxyfylline, N-acetylcysteine (NAC), Procysteine,  $\alpha$ -trichosanthin, phosphonoformic acid, as well as immunomodulators such as interleukin II or thymosin, granulocyte macrophage colony stimulating factors,

erythropoetin, soluble CD<sub>4</sub> and genetically engineered derivatives thereof, or non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as nevirapine (BI-RG-587), loviride (α -APA) and delavuridine (BHAP), and phosphonoformic acid, 5 and 1,4-dihydro-2H-3,1-benzoxazin-2-ones NNRTIs such as (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one (L-743,726 or DMP-266), and quinoxaline NNRTIs such as isopropyl (2S)-7-fluoro-3,4-dihydro-2-ethyl-3-oxo-1(2H)-quinoxalinecarboxylate 10 (HBY1293).

More preferably the combination therapy involves the administration of one of the above mentioned agents and a compound within one of the preferred or particularly preferred sub-groups within formula (I) as described above. 15 Most preferably the combination therapy involves the joint use of one of the above named agents together with one of the compounds of formula (I) specifically named herein.

The present invention further includes the use of a compound according to the invention in the manufacture of 20 a medicament for simultaneous or sequential administration with at least one other therapeutic agent, such as those defined hereinbefore.

In order that this invention may be more fully understood, the following examples are set forth. These 25 examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

EXAMPLESGeneral Methods and Conditions

All temperatures are recorded in degrees Celsius.

5 Thin layer chromatography (TLC) was carried out using 0.25 mm thick E. Merck silica gel 60 F<sub>254</sub> plates and elution with the indicated solvent system. Detection of the compounds was carried out by treating the plate with an appropriate visualizing agent, such as 10% solution of phosphomolybdc acid in ethanol or a 0.1% solution of ninhydrin in ethanol, followed by heating, and/or by exposure to UV light or iodine vapors when appropriate. Thick layer silica gel chromatography was also carried out using E. Merck 60 F<sub>254</sub> plates ("prep plates") of 0.5, 1.0, or 2.0 mm thickness.

10

15 Following development of the plate, the band of silica containing the desired compound was isolated and eluted with an appropriate solvent. Analytical HPLC was carried out using a Water's Delta Pak, 5  $\mu$ M silica, C18 reversed-phase column, 3.9 mm ID x 15 cm L with a flow rate of 1.5 mL/min

20 using the following table:

Mobile phase: A = 0.1% CF<sub>3</sub>CO<sub>2</sub>H in H<sub>2</sub>O

B = 0.1% CF<sub>3</sub>CO<sub>2</sub>H in CH<sub>3</sub>CN

Gradient: T = 0 min., A (95%), B (5%)

25 T = 20 min., A (0%), B (100%)

T = 22.5 min., A (0%), B (100%)

Preparative HPLC was also carried out using C<sub>18</sub> reversed-phase media. HPLC retention times were recorded in minutes.

30 NMR spectral data was recorded using a Bruker AMX500, equipped with either a reverse or QNP probe, at 500 MHz, and was taken in the indicated solvent.

We have measured the inhibition constants of each compound against HIV-1 protease using the method described

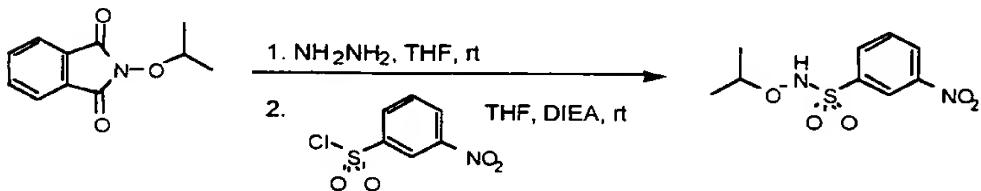
essentially by M.W. Pennington et al., Peptides 1990, Gimel, E. and D. Andrew, Eds., Escom, Leiden, Netherlands (1990); and the method described essentially by Partaledis et al., J. Virol., 69, pp. 5228-35 (1995).

5 Compounds of invention were tested for their antiviral potency in several virological assays.

Insofar as the compounds of this invention are able to inhibit the replication of the HIV virus in  $CD_4^+$  cells of human lineage, they are of evident clinical utility 10 for the treatment of HIV infection. These tests are predictive of the compounds ability to inhibit HIV protease in vivo.

#### Example 1

15 Step 1:

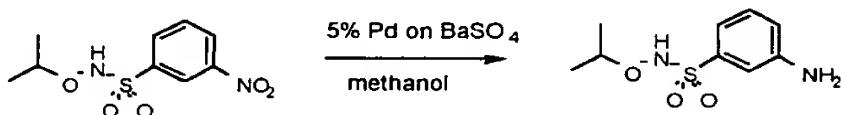


15 **N'-isopropoxy-3-nitro-1-benzenesulfonamide.** To a cooled solution ( $0^\circ C$ ) of O-isopropyl hydroxypythalimide (4.10 g, 0.02 mol) in anhydrous THF (45 mL) was added anhydrous hydrazine (0.69 mL, 0.022 mmol) with stirring. The solution was allowed to warm to RT and stir for 20.0h, filtered and the ppt. was washed with anhydrous THF (20 mL). To the filtrate was added 3-nitro-benzenesulfonylchloride (4.86 g, 0.022 mol) and diisopropylethylamine (4.17 mL, 0.024 mol) at RT and the mixture was stirred at RT for 20h. The solution was evaporated and the residue was partitioned between ethyl acetate (200 mL) and Aq. 1.0N HCl (30 mL). The organic layer was washed with 1.0N HCl (2 x 50 mL), 5% Aq.  $NaHCO_3$  (2 x 50 mL), brine (2 x 25 mL), dried ( $MgSO_4$ ),

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filtered, and evaporated to give a yellow oil. The oil was purified by column chromatography: hexane/ethyl acetate (80/20) to give 3.58g (69%) of the product as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.20 (d, 6H); 4.27 (m, 1H); 7.05 (s, 1H); 7.75 (l, 1H); 8.22 (d, 1H); 8.48 (dd, 1H); 8.74 (t, 1H).

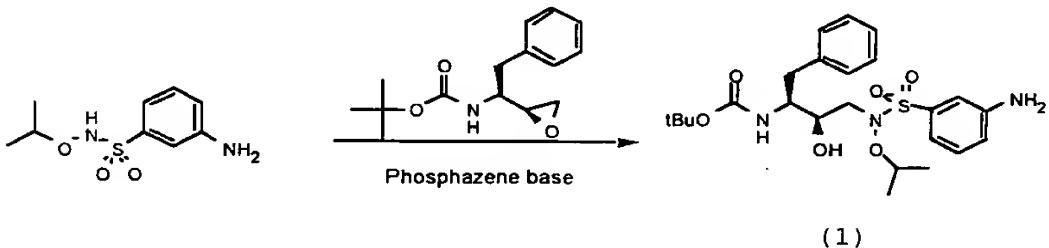
5 Step 2:



10 **3-amino-N<sup>1</sup>-isopropoxy-1-benzenesulfonamide.** To a Parr H<sub>2</sub>

vessel containing 5% Pd/BaSO<sub>4</sub> (0.350g) was added a methanolic solution (125 mL) of N<sup>1</sup>-isopropoxy-3-nitro-1-benzenesulfonamide (3.50 g, 0.0135 mol) at rt under Ar atm. The solution was hydrogenated at 45psi for approx. 1.0 h. The reaction mixture was filtered (1/2" celite pad) and evaporated to give the product as yellow crystalline solid 2.90 g (96%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.20 (d, 25H); 4.27 (m, 1H); 7.05 (s, 1H); 7.75 (l, 1H); 8.22 (d, 1H); 8.48 (dd, 1H); 8.74 (t, 1H).

15 20 Step 3:



25 **tert-butyl-N-(1S,2R)-3-[(3-aminophenyl)sulfonyl]**

**(isopropoxy) amino]-1-benzyl-2-hydroxypropylcarbamate.** To a solution of 3-amino-N<sup>1</sup>-isopropoxy-1-benzenesulfonamide (2.20

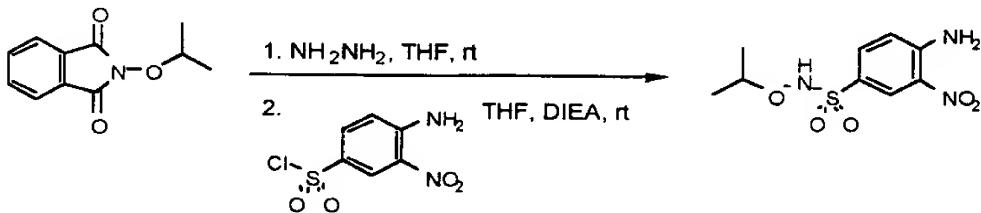
g, 9.56 mmol) and *tert*-butyl *N*-(1*S*)-1-[(2*S*)oxiran-2-yl]-2-phenylethylcarbamate (2.01 g, 7.65 mmol) in anhydrous THF (10.0 mL) was added phosphazene base P4 *t*-butyl solution (1.0 M in hexanes, 1.53 mL, 1.53 mmol) with stirring at rt.

5 After 8.0h at rt, the THF was evaporated to give a dark yellow residue that was dissolved in ethyl acetate (200 mL). This solution was washed with 0.50M HCl (3 x 20.0 mL), sat. NaHCO<sub>3</sub> (3 x 20 mL), brine (2 x 25 mL), dried (MgSO<sub>4</sub>), filtered, and evaporated to give a yellow foam. The crude 10 product was purified by column chromatography: methylene chloride/ethyl acetate (95/5) to give the product as a light yellow foam (3.61g, 95%). MS: product: M+Na = 516 <sup>1</sup>H NMR (CD<sub>3</sub>OD) 0.90(m, 15H); 2.50-3.10(m, 4H); 3.60-3.85(m, 2H); 4.70(m, 1H); 6.90(d, 1H); 7.05(d, 1H); 7.10-7.30(m, 6H).

15

Example 2

Step 1:

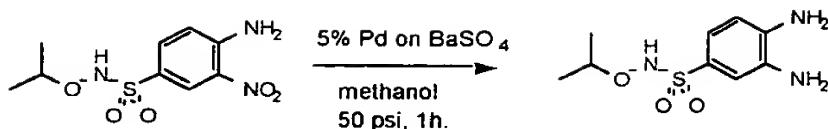


20 **4-amino-*N*<sup>1</sup>-isopropoxy-3-nitro-1-benzenesulfonamide.**

Prepared using the procedure outlined in Example 1. The crude product was purified by column chromatography: 60/40 hexane/ethyl acetate to give the product as a yellow solid (63%). <sup>1</sup>H NMR (DMSO) 1.05(d, 6H); 4.00(m, 1H); 7.10(d, 1H); 25 7.65(d, 1H); 8.10(s, 2H); 8.40(s, 1H).

Step 2:

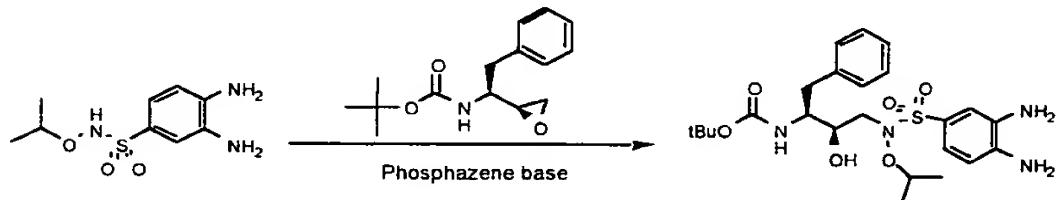
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**3,4-diamino-N¹-isopropoxy-1-benzenesulfonamide.** Prepared using the procedure outlined in Step 2, Example 1. <sup>1</sup>H NMR (DMSO) 1.05(d, 6H); 3.95(m, 1H); 4.80(s, 2H); 5.30(s, 2H); 6.50(d, 1H); 6.92(d, 1H); 7.97(s, 1H); 9.50(s, 1H).

5

Step 3:



10

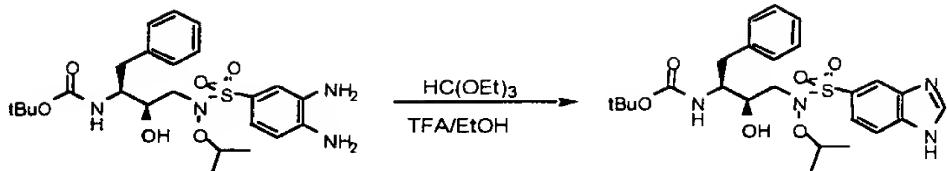
(2)

**tert-butyl-N-(1S,2R)-1-benzyl-3-[(3,4-diaminophenyl)sulfonyl](isopropoxy)amino]-2-hydroxypropyl carbamate.** Prepared using the procedure outlined in Step 3, Example 1. The product was purified by column chromatography: to 40/60 hexane/ethyl acetate give the product as a dark orange solid (91%). MS: M+Na = 531 <sup>1</sup>H NMR (CD<sub>3</sub>OD) 0.90(m, 15H); 2.50-3.10(m, 4H); 3.60-3.85(m, 2H); 4.45(m, 1H); 6.40(d, 1H); 6.70(d, 1H); 7.00-7.30(m, 6H).

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Example 3

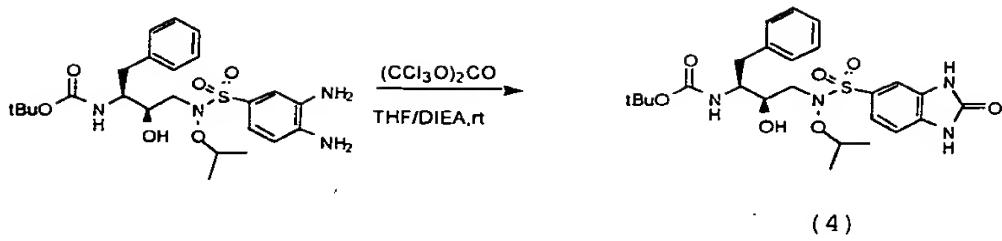
(3)

5 **tert-butyl-N-(1S,2R)-3-[(1H-1,3-benzimidazol-5-ylsulfonyl)(isopropoxy)amino]-1-benzyl-2-hydroxypropylcarbamate.** To a solution of *tert*-butyl *N*-(1*S*,2*R*)-1-benzyl-3-[(3,4-diaminophenyl)sulfonyl](isopropoxy)amino]-2-hydroxy propylcarbamate (0.70 g, 1.38 mmol) in ethanol (10 mL) was added triethylorthoformate (0.64 mL, 3.86 mmol) and TFA (5.0  $\mu$ L) with stirring at rt. After 1.0h., the reaction was neutralized with Aq. sat. NaHCO<sub>3</sub> (50  $\mu$ L) and evaporated to give an orange residue. The residue was dissolved in ethyl acetate (100 mL) and washed with aq. sat. NaHCO<sub>3</sub> (1 x 20 mL), water (2 x 20 mL), brine (1 x 20 mL), dried (MgSO<sub>4</sub>), filtered, and evaporated to give the crude product as a orange foam. The crude product was purified by column chromatography: 30/70 hexane/ethyl acetate give the product as a white solid (0.60g, 85%).

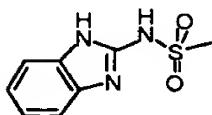
10 15 MS: M+H = 519 <sup>1</sup>H NMR (CD<sub>3</sub>OD) 1.00-1.40(m, 15H); 2.50-3.10(m, 4H); 3.60-3.85(m, 2H); 4.60(m, 1H); 7.20(m, 5H); 7.80(s, 2H); 8.20(s, 1H); 8.40(s, 1H).

20

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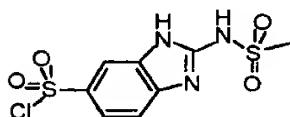
Example 4

5 **tert-butyl-N-((1S,2R)-1-benzyl-2-hydroxy-3-isopropoxy[ (2-  
oxo-2,3-dihydro-1H-1,3-benzimidazol-5-  
yl)sulfonyl]aminopropyl)carbamate.** To a solution of *tert*-  
butyl *N*-(1*S*,2*R*)-1-benzyl-3-[(3,4-diaminophenyl)sulfonyl]  
(isopropoxy)amino]-2-hydroxypropyl carbamate (0.70 g, 1.38  
10 mmol) and DIEA (0.24 mL, 1.38 mmol) in anhydrous THF (10 mL)  
was added triphosgene (0.136 g, 0.46 mmol) with stirring at  
rt. After 0.5h., the THF was removed *in vacuo* and the  
residue was dissolved in ethyl acetate (100 mL). This  
solution was washed with 0.5M HCl (2 x 25 mL), aq. sat.  
15 NaHCO<sub>3</sub> (2 x 25 mL), brine (1 x 25 mL), dried (MgSO<sub>4</sub>), filtered  
and evaporated to give the crude product. The crude product  
was purified by column chromatography: 30/70 hexane/ethyl  
acetate give the product as a yellow solid (0.63g, 86%)  
MS: M+Na = 557 <sup>1</sup>H NMR (CD<sub>3</sub>OD) 1.00-1.40(m, 15H); 2.50-  
20 3.10(m, 4H); 3.60-3.85(m, 2H); 4.55(m, 1H); 7.20(m, 6H);  
7.50(m, 2H).

Example 525 **Step 1:**

**N-methanesulfonyl-2-aminobenzimidazole.** 2-amino-benzimidazole (1.0 g, 7.5 mmol) was dissolved in 15 mL of anhydrous  $\text{CH}_2\text{Cl}_2$  and 3 mL anhydrous DMF and cooled to  $\sim 0^\circ\text{C}$ . Triethylamine (1.6 mL, 1.5 eq.) was added followed by an 5 addition of methanesulfonylchloride (580  $\mu\text{L}$ , 7.5 mmol) over  $\sim 1$  minute. After 1 minute at  $\sim 0^\circ\text{C}$ , the reaction was warmed to RT. After 1 hour the reaction was quenched with water, and partitioned between a saturated sodium bicarbonate solution and  $\text{CH}_2\text{Cl}_2$ . The aqueous layer was 10 extracted with  $\text{CH}_2\text{Cl}_2$  and the combined organic layers were washed with water (2 times), brine then dried over  $\text{NaSO}_4$ , filtered and the solvent was removed *in vacuo* to give 455 mg of N-methanesulfonyl-2-aminobenzimidazole. HPLC shows the material to be 91% pure, (ret. time = 3.70). LCMS : obs. 15  $\text{M}+\text{H}^+$  212.1 amu. The material was carried on without purification.

## Step 2:



20 **N-methanesulfonyl-5-chlorosulfonyl-2-aminobenzimidazole.** To 9.5 mL (20 eq., 142 mmol) of well stirred chlorosulfonic acid at  $\sim 25^\circ\text{C}$  was added N-methanesulfonyl-2-aminobenzimidazole (1.5 g, 7.1 mmol) in small portions over 25 10 minutes with slight exotherming. The solution was stirred at  $\sim 25^\circ\text{C}$  for 3.5 hours, then was added dropwise to a well stirred mixture of ice and water. The aqueous solution was slowly basified to pH  $\sim 7.5$  with solid sodium bicarbonate and extracted with  $\text{EtOAc}$ . A precipitate formed 30 in the organic phase which was filtered off and was washed

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with H<sub>2</sub>O and dried on the filter to yield 1.23 g of N-methanesulfonyl-5-chlorosulfonyl-2-aminobenzimidazole. HPLC, single peak, ret. time = 7.61 min. MS: Obs. M + H @ 310.0 amu.

5

Step 3:



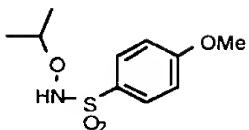
*tert*-Butyl-N-((1*S*,2*R*)-1-benzyl-3-(isopropoxy) (2-

10 [ (methylsulfonyl)amino]benzimidazol-5-ylsulfonyl)amino-2-  
hydroxypropyl) carbamate. *tert*-Butyl-N-((1*S*,2*R*)-1-benzyl-3-  
(isopropoxy)amino-2-hydroxypropyl)carbamate (86 mg, 0.25  
mmol) was combined with 2-[(methylsulfonyl)amino]  
15 benzimidazol-5-ylsulfonyl chloride (77 mg, 0.25 mmol) in  
anhydrous pyridine (1 ml) with a catalytic amount of N,N-  
dimethylaminopyridine. The reaction was stirred at room  
temperature overnight. The solvent was evaporated under  
vacuum. The crude mixture was diluted in EtOAc and washed  
with water and brine. Organic phase was dried with MgSO<sub>4</sub>  
20 and solvent was removed in vacuo. Purification by TLC prep  
(2% MeOH/CH<sub>2</sub>Cl<sub>2</sub>). Recovered 56 mg (37%) of product as a  
white solid. HPLC showed the material to be 98% pure; Ret.  
time = 9.87 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.12-8.04 (m, 8H), 6.5 (m,  
1H), 4.47-4.51 (m, 2H), 3.68 (m, 2H), 3.22 (s, 3H), 2.81-  
2.88 (m, 3H), 1.75 (m, 2H), 1.22 (s, 9H), 1.16 (d, 6H). MS  
25 (ES+): obs. M+H @ 612.1 amu.

- 75 -

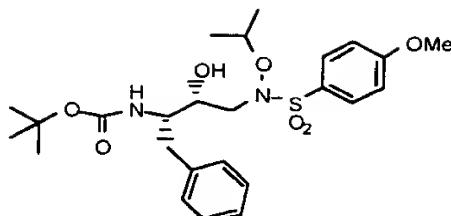
Example 6

Step 1:



5 ***N<sup>1</sup>-(isopropoxy)-4-methoxy-1-benzenesulfonamide.*** A vigorously stirred solution of 2-isopropoxy-1*H*-isoindole-1,3(2*H*)-dione [2.50 g, 12.2 mmol, Synth. Comm., 22(10), 1427-1432 (1992)] in 35 mL of tetrahydrofuran under an Argon atmosphere at ambient temperature was treated with anhydrous hydrazine 10 (0.421 mL, 13.41 mmol). After 1.5 hours, 4-methoxybenzenesulphonyl chloride (3.024 g, 14.63 mmol), dichloromethane (20 mL) and *N,N*-diisopropylethylamine (6.38 mL, 36.6 mmol) was added with continued stirring. After an additional 2 hours at ambient temperature, the reaction 15 mixture was evaporated *in vacuo* to a residue and partitioned between ethyl acetate and 1N hydrochloric acid. The layers were separated and the aqueous layer was extracted again with ethyl acetate. The combined organic layers were washed with 5% w/v potassium carbonate and brine, dried over anhydrous magnesium sulfate, filtered and evaporated 20 *in vacuo* to a residue. The crude material was purified on flash grade silica gel eluting with 30% ethyl acetate in hexane. Fractions containing the product were combined, evaporated *in vacuo*, and dried under high vacuum to provide 25 *N<sup>1</sup>-(isopropoxy)-4-methoxy-1-benzenesulfonamide* (2.061 g, 69%) as a white solid. *H*1-NMR (chloroform-D3): 1.22 (d, 6H), 3.92 (s, 3H), 4.27 (m, 1H), 6.70 (s, 1H), 7.05 (d, 2H), 7.90 (d, 2H). MS(ESI): 268 (M+Na).

30 Step 2:



(6)

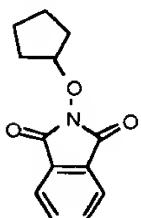
**tert-butyl N-((1S,2R)-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate.** A solution of *N*<sup>i</sup>-(isopropoxy)-4-methoxy-1-benzenesulfonamide (0.147 g, 0.599 mmol) and *tert*-butyl *N*-(1*S*)-1-[(2*S*)oxiran-2-yl]-2-phenylethylcarbamate (75 mg, 0.285 mmol) in anhydrous tetrahydrofuran (1 mL) under an Argon atmosphere was treated with phosphazene base P<4>t-Bu (0.285 mL, 0.285 mmol, 1.0 M in hexane). After stirring for 30 minutes at ambient temperature, the reaction mixture was quenched with several drops of glacial acetic acid and evaporated *in vacuo* to a residue. The crude product was purified on a preparative TLC plate (20x20, 500  $\mu$ M) eluting with 35:65 ethyl acetate : hexane. The product band was removed, eluted with ethyl acetate, and evaporated *in vacuo* to a residue. The crude product was purified again on a preparative TLC plate (20x20, 1000  $\mu$ M) eluting with 4:1 dichloromethane : ethyl acetate. The product band was removed, eluted with ethyl acetate, and evaporated *in vacuo*. The residue was triturated with water and the resulting slurry was stirred overnight, filtered, and dried under high vacuum to provide *tert*-butyl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate (87 mg, 60%) as a white solid. *H*<sub>1</sub>-NMR (methanol-D<sub>4</sub>): 1.22 (s, 9H), 1.24 (d, 6H), 2.52 (m, 2H), 3.07 (m, 2H), 3.68 (m, 2H),

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3.87 (s, 3H), 4.50 (m, 1H), 7.08 (m, 2H), 7.19 (m, 5H), 7.75 (m, 2H). MS (ESI): 531 (M+Na).

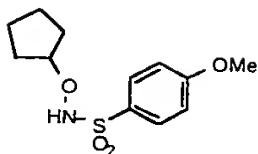
Example 7

5 Step 1:



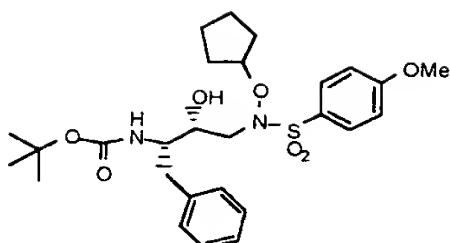
2-(cyclopentyloxy)-1H-isoindole-1,3(2H)-dione. A mixture of N-hydroxyphthalimide (10.00g, 61.3 mmol), cyclopentylbromide (8.21 mL, 76.63 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (13.75 mL, 76.6 mmol) were combined under an Argon atmosphere in dimethylformamide (50 mL). The mixture was heated to 55°C and stirred vigorously for 1.5 hours. After cooling to ambient temperature, the solvent was removed *in vacuo* and the residue was partitioned between ethyl acetate and 1N hydrochloric acid. After separating the phases, the aqueous layer was extracted again with ethyl acetate. The combined organic layers were washed with 5% w/v potassium carbonate, saturated aqueous brine, dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The residue was triturated with hexane, filtered, and dried under high vacuum to provide 2-(cyclopentyloxy)-1H-isoindole-1,3(2H)-dione (11.37 g, 80%).  $^1\text{H-NMR}$  (chloroform-D3): 1.61 (m, 2H), 1.77 (m, 2H), 1.97 (m, 4H), 4.91 (m, 1H), 7.73 (m, 2H), 7.82 (m, 2H). MS (ESI): 254 (M+Na).

Step 2:



***N<sup>1</sup>-(cyclopentyloxy)-4-methoxy-1-benzenesulfonamide.*** A mixture of 2-(cyclopentyloxy)-1*H*-isoindole-1,3(2*H*)-dione (3.00 g, 12.99 mmol) in anhydrous tetrahydrofuran (15 mL) at ambient temperature under an Argon atmosphere was treated with anhydrous hydrazine (0.448 mL, 14.29 mmol). After stirring vigorously for 1.5 hours, the resulting slurry was filtered and washed with approximately 15 mL of anhydrous tetrahydrofuran. The filtrate was combined with 4-methoxybenzenesulphonyl chloride (2.95 g, 14.29 mmol) and *N,N*-diisopropylethylamine (2.72 mL, 15.6 mmol). After stirring at ambient temperature for approximately 18 hours, the reaction mixture was evaporated *in vacuo* to a residue and partitioned between ethyl acetate and 1*N* hydrochloric acid. The layers were separated and the organic phase was extracted again with ethyl acetate. The combined organic layers were washed with 5% w/v potassium carbonate and brine, dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo* to a residue. The crude material was purified on flash grade silica gel eluting with 15:85 ethyl acetate : hexane. Fractions containing the product were combined, evaporated *in vacuo*, and dried under high vacuum to provide *N<sup>1</sup>-(cyclopentyloxy)-4-methoxy-1-benzenesulfonamide* (2.771 g, 79%) as an oil. *H*1-NMR (chloroform-D3): 1.61 (m, 8H), 3.87 (s, 3H), 4.57 (m, 1H), 6.67 (s, 1H), 6.99 (m, 2H), 7.83 (m, 2H). MS(ESI): 294 (M+Na).

30 Step 3:



(7)

**tert-butyl N-((1S,2R)-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate.** A

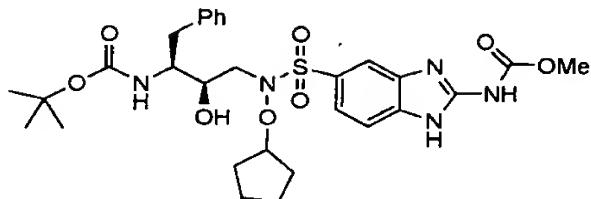
5 solution of *N*-(cyclopentyloxy)-4-methoxy-1-benzenesulfonamide (1.005 g, 3.71 mmol) and *tert*-butyl *N*-(1*S*)-1-[(2*S*)oxiran-2-yl]-2-phenylethylcarbamate (0.780 g, 2.97 mmol) in anhydrous tetrahydrofuran (5 mL) under an Argon atmosphere was treated with phosphazene base P<sub>t</sub>/4-t-Bu (0.593 mL, 0.593 mmol, 1.0 M in hexane). The mixture was stirred at ambient temperature for 2.5 hours and then quenched with several drops of glacial acetic acid. The solution was evaporated *in vacuo* to a residue and partitioned between ethyl acetate and 1N hydrochloric acid. 10 After separating the phases, the aqueous layer was extracted with ethyl acetate. The combined ethyl acetate layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified on flash grade silica gel eluting with 9:1 hexane ethyl acetate (0.5 L), 85:15 hexane ethyl acetate (0.5 L), and finally 4:1 hexane ethyl acetate (1.5 L). Fractions containing the product were combined, evaporated *in vacuo* and dried under high vacuum to provide *tert*-butyl *N*-(1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl) 15 sulfonyl]amino-2-hydroxypropyl)carbamate (1.418 g, 89%) as a foam. *H*1-NMR (chloroform-D3): 1.38 (s, 9H), 1.70 (m, 8H), 2.98 (m, 4H), 3.85 (bm, 2H), 3.92 (s, 3H), 4.61 (bs, 1H), 20

- 80 -

4.85 (m, 1H), 7.02 (m, 2H), 7.29 (m, 5H), 7.76 (m, 2H).  
MS (ESI): 535 (MH<sup>+</sup>).

Example 8

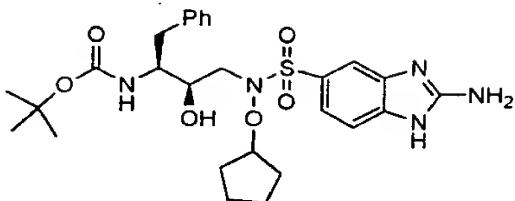
5 Step 1:



10 **Tert-butyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy) (2-[(methoxycarbonyl)amino]-1H-benzimidazol-5-ylsulfonyl)amino]-2-hydroxypropylcarbamate.** Tert-butyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)amino]-2-hydroxypropylcarbamate (Step 1, Example 54) (1.73 g, 4.75 mmol), methyl N-[5-(chlorosulfonyl)-1H-benzimidazol-2-yl]carbamate (1.37g, 4.75 mmol), anhydrous diisopropylethylamine (0.83 mL, 4.75 mmol), and N,N-dimethylaminopyridine (170 mg, 1.42 mmol) were combined in anhydrous tetrahydrofuran (15 mL) and anhydrous N,N-dimethylformamide (8 mL) in a 50 mL round bottomed flask under nitrogen. The reaction was stirred for 24 hours and concentrated in vacuo. After the workup described in Step 20, Example 54, the product was isolated as a white foam (2.56 g, 4.14 mmol) and used directly without further purification. <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ: 7.60-6.64 (m, 9H), 5.11 (d, J=6.1 Hz, 1H), 4.83 (bs, 1H), 3.81 (s, 3H), 3.54-1.42 (m, 14H), 1.15 (s, 9H). MS (ES): 618 (M+1), 616 (M-1).

25

Step 2:



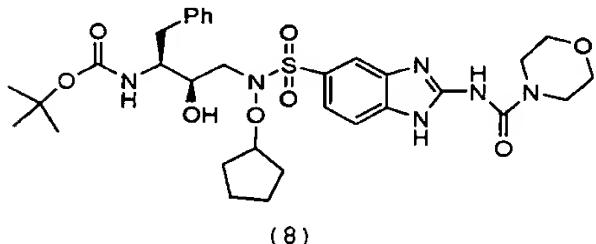
**Tert-butyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)(2-amino-1H-benzimidazol-5-ylsulfonyl)amino]-2-hydroxypropylcarbamate.**

Tert-butyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)(2-[(methoxycarbonyl)amino]-1H-

5 benzimidazol-5-ylsulfonyl)amino]-2-hydroxypropylcarbamate (Step 1, above) (2.52 g, 4.08 mmol) and lithium iodide  
hydrate (2.60 g, 19.4 mmol) were dissolved in pyridine (15 mL) in a 50 mL round bottomed flask and heated at 100°C for  
10 8 hours. The reaction was allowed to cool and then  
concentrated in vacuo. After the workup described in Step  
3, Example 54, the product was purified by silica gel flash  
chromatography using a gradient elution of chloroform:  
methanol: water (90:10:0 to 10:3:0.5) to yield a beige  
15 powder (1.75 g, 3.13 mmol, 77%). <sup>1</sup>H NMR (d<sub>6</sub>-DMSO) δ: 7.50-  
6.64 (m, 9H), 5.07 (d, J=6.0 Hz, 1H), 4.80 (bs, 1H), 3.56-  
1.40 (m, 16H), 1.18 (s, 9H). MS(ES): 560 (M+1), 558 (M-1).

**Step 3:**

20



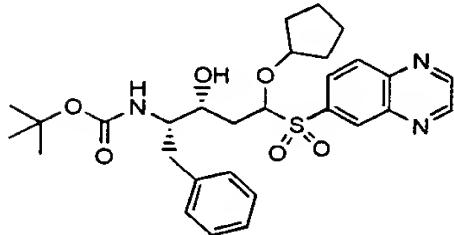
**Tert-butyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)(2-[(N-**

25 **morpholinocarbonyl)amino]-1H-benzimidazol-5-ylsulfonyl)amino]-2-hydroxypropylcarbamate.** Tert-butyl N-

(1*S*,2*R*)-1-benzyl-3-[(cyclopentyloxy)(2-amino-1*H*-benzimidazol-5-ylsulfonyl)amino]-2-hydroxypropylcarbamate (Step 2, above) (300 mg, 0.536 mmol), 4-morpholine carbonyl chloride (0.08 mL, 0.643 mmol), and anhydrous

5 diisopropylethylamine (0.11 mL, 0.643 mmol), were combined in anhydrous tetrahydrofuran (8 mL) in a 25 mL round bottomed flask under nitrogen. The reaction was refluxed for 18 hours, allowed to cool, and concentrated in vacuo. After the workup described in Step 3, Example 54, the 10 residue was purified by preparative silica gel TLC using 90:10 chloroform: methanol as an eluent to give the product as a beige solid (70 mg, 0.104 mmol, 20%).  $^1\text{H}$  NMR ( $\text{d}_6$ -DMSO)  $\delta$ : 7.54-6.65 (m, 8H), 5.11 (d,  $J=6.0$  Hz, 1H), 4.81 (bs, 1H), 3.82-1.40 (m, 23H), 1.17 (s, 9H). MS(ES): 673 (M+1), 15 671 (M-1).

Example 9



20 (9)

**Preparation of tert-butyl N-[(1*S*,2*R*)-1-benzyl-4-(cyclopentyloxy)-2-hydroxy-4-(6-quinoxalinylsulfonyl)butyl]carbamate.** A mixture of tert-25 butyl N-[(1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)][(3,4-diaminophenyl)sulfonyl]amino-2-hydroxypropylcarbamate (Example 10), (750 mg, 1.41 mmol) and 1,5-dioxane-2,3-diol (219 mg, 1.83 mmol) were combined under Argon in absolute

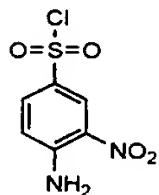
- 83 -

ethanol (3 mL) at ambient temperature. After stirring for approximately 11 days, the reaction was evaporated in vacuo and the residue was purified on flash grade silica gel eluting with ethyl acetate : hexane (1:1). Fractions 5 containing the product were combined, evaporated in vacuo and dried under high vacuum to provide *tert*-butyl *N*-[(1*S*,2*R*)-1-benzyl-4-(cyclopentyloxy)-2-hydroxy-4-(6-quinoxalinylsulfonyl)butyl]carbamate as a yellow foam (696 mg, 89%). An analytical sample was prepared by purification 10 of 75 mg on a preparative TLC plate (20X20 cm, 1000  $\mu$ M) eluting with 95:5 dichloromethane : methanol. The product band was removed, eluted with 4:1 methylene chloride : methanol, filtered, and evaporated in vacuo. The residue was triturated with water and filtered to provide *tert*-butyl 15 15 N-[(1*S*,2*R*)-1-benzyl-4-(cyclopentyloxy)-2-hydroxy-4-(6-quinoxalinylsulfonyl)butyl]carbamate as a white solid.  $^1$ H-NMR (dimethylsulfoxide-D6): 1.05 (s, 9H), 1.74 (m, 8H), 2.47 (m, 1H), 2.73 (m, 1H), 3.07 (m, 2H), 3.55 (m, 2H), 4.90 (m, 1H), 5.24 (m, b, 1H), 6.68 (d, 1H), 7.19 (m, 5H), 8.15 (m, 1H), 8.39 (m, 1H), 8.49 (s, 1H), 9.18 (m, 2H). MS(ESI): 20 579 (M+Na).

Example 10

Step 1:

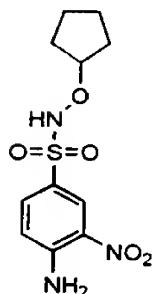
25



o-nitroaniline-p-sulfonyl chloride. A mixture of o-nitroaniline-p-sulfonic acid sodium salt (25.00 g, 104 mmol) 30 and phosphoryl chloride (75 mL, 804 mmol) under Argon was

heated to reflux and vigorously stirred for 4 hours. After cooling to ambient temperature, the reaction mixture was carefully added to a large excess of ice. The resulting slurry was stirred for 15 min., filtered and dried under 5 vacuum to provide *o*-nitroaniline-*p*-sulfonyl chloride (21.43 g, 87%) as a yellow solid.  $^1\text{H-NMR}$  (dimethylsulfoxide-D6): 5.8 (b, 2H), 6.97 (d, 1H,  $J = 8.8$ ), 7.57 (m, 1H), 8.18 (d, 1H,  $J = 2.0$ ).

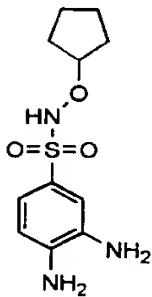
10 Step 2:



15 **4-amino-N-(cyclopentyloxy)-3-nitrobenzenesulfonamide.** A solution of 2-(cyclopentyloxy)-1*H*-isoindole-1,3(2*H*)-dione (10.00 g, 43.30 mmol) in anhydrous tetrahydrofuran (100 mL) at ambient temperature under an Argon atmosphere was treated with anhydrous hydrazine (1.49 mL, 47.63 mmol). After stirring vigorously for 2.5 hours, the resulting slurry was 20 filtered and washed with approximately 20 mL of anhydrous tetrahydrofuran. The filtrate was combined with *o*-nitroaniline-*p*-sulfonyl chloride (11.26 g, 47.63 mmol) and N,N-diisopropylethylamine (9.05 mL, 51.96 mmol) and stirred under an Argon atmosphere for 16 hrs. at ambient 25 temperature. The reaction mixture was diluted with 1N NaHSO<sub>4</sub> and dichloromethane and transferred to a separatory funnel. The organic phase was separated and the aqueous layer was extracted twice with dichloromethane. The

combined organic layers were washed with 5% aqueous potassium carbonate, dried over anhydrous magnesium sulfate, filtered through a pad of diatomaceous earth and evaporated *in vacuo*. The residue was purified on flash grade silica 5 gel eluting with 1:1 ethyl acetate : hexane. Fractions containing the product were combined, evaporated *in vacuo* to a residue and triturated with hexane. The slurry was filtered and the product was dried under high vacuum to provide 4-amino-*N*-(cyclopentyloxy)-3-nitrobenzenesulfonamide 10 (8.89 g, 68%) as a yellow solid.  $^1\text{H-NMR}$  (chloroform-D3): 1.57 (m, 4H), 1.74 (m, 4H), 4.61 (m, 1H), 6.52 (b, 2H), 6.73 (s, 1H), 6.90 (d, 1H), 7.79 (m, 1H), 8.70 (d, 1H). MS(ESI): 324 (M+Na).

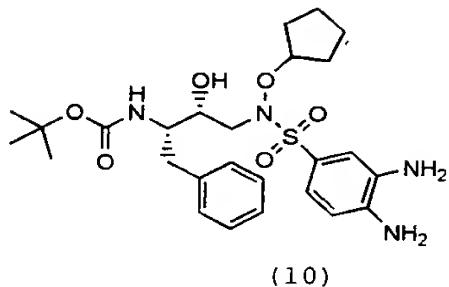
15 Step 3:



3,4-diamino-*N*-(cyclopentyloxy)benzenesulfonamide. A solution of 4-amino-*N*-(cyclopentyloxy)-3-20 nitrobenzenesulfonamide (4.50 g, 14.95 mmol) in 1:1 ethyl acetate : ethanol (150 mL) was combined with 5% Pd on barium sulfate and reduced under a hydrogen atmosphere over 72 hours. The reaction mixture was filtered through a pad of diatomaceous earth and evaporated *in vacuo* to a residue 25 which crystallized on standing. The solid was slurried in hexane, filtered and dried under high vacuum to provide 3,4-diamino-*N*-(cyclopentyloxy)benzenesulfonamide (4.086 g, 100%).

as a light brown solid H1-NMR (dimethylsulfoxide-D6): 1.61 (m, 8H), 4.37 (m, 1H), 4.90 (b, 2H), 5.38 (b, 2H), 6.57 (d, 1H), 6.88 (m, 1H), 6.96 (d, 1H), 9.64 (s, 1H). . MS(ESI): 272 (M+H). .

5 Step 4:



10 **tert-butyl N-((1S,2R)-1-benzyl-3-(cyclopentyloxy)(3,4-diaminophenyl)sulfonyl)amino-2-hydroxypropyl carbamate.** A solution of 3,4-diamino-N-(cyclopentyloxy)benzenesulfonamide (2.00 g, 7.38 mmol) and *tert*-butyl N-(1*S*)-1-[(2*S*)oxiran-2-yl]-2-phenylethylcarbamate (1.553 g, 5.90 mmol) in anhydrous tetrahydrofuran (10 mL) under an Argon atmosphere was  
 15 treated with phosphazene base P<sub>t</sub>/4<sub>t</sub>-Bu (1.2 mL, 1.2 mmol, 1.0 M in hexane). After stirring at ambient temperature for approximately 18 hours, the reaction mixture was quenched with several drops of glacial acetic acid and evaporated *in vacuo*. The residue was partitioned between ethyl acetate  
 20 and 1N aqueous sodium hydrogen sulfate. After separating the layers, the organic phase was washed with 5% w/v aqueous potassium carbonate, brine, dried over anhydrous sodium sulfate and evaporated *in vacuo* to a residue. The crude product was purified on flash grade silica gel eluting with  
 25 3:2 ethyl acetate : hexane. Fractions containing the product were combined, evaporated *in vacuo* and dried under high vacuum to provide *tert*-butyl N-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)(3,4-diaminophenyl)sulfonyl)amino-2-hydroxypropyl carbamate (2.553 g, 65%) as a foam. H1-NMR

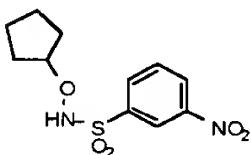
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(chloroform-D3): 1.33 (s, 9H), 1.53 (m, 4H), 1.74 (m, 4H), 2.91 (m, 3H), 3.04 (m, 1H), 3.61 (b, 4H), 3.79 (m, 2H), 4.58 (m, 1H), 4.77 (m, 1H), 6.69 (d, 1H), 7.09 (s, 1H), 7.22 (m, 7H). MS (ESI): 535 (M+H).

5

Example 11

Step 1:

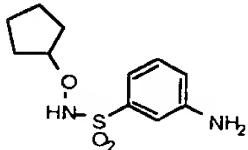


***N<sup>1</sup>-(cyclopentyloxy)-3-nitro-1-benzenesulfonamide.*** A mixture of 2-(cyclopentyloxy)-1*H*-isoindole-1,3(2*H*)-dione (3.00 g, 12.99 mmol) in anhydrous tetrahydrofuran (25 mL) under an Argon atmosphere was treated with anhydrous hydrazine (0.448 mL, 14.29 mmol). After stirring vigorously for 2.5 hours, the resulting slurry was filtered and washed with approximately 15 mL of anhydrous tetrahydrofuran. The filtrate was combined with 3-nitro-1-benzenesulphonyl chloride (3.17 g, 14.29 mmol) and *N,N*-diisopropylethylamine (2.72 mL, 15.6 mmol). After stirring at ambient temperature for approximately 18 hours, the reaction mixture was evaporated *in vacuo* to a residue and partitioned between ethyl acetate and 1N hydrochloric acid. The phases were separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with 5% w/v potassium carbonate and brine, dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo* to a residue. The crude material was purified on flash grade silica gel eluting with 15:85 ethyl acetate : hexane. Fractions containing the product were combined, evaporated *in vacuo*, and dried under high vacuum to provide *N<sup>1</sup>-(cyclopentyloxy)-3-nitro-1-benzenesulfonamide* (3.224 g, 87%).

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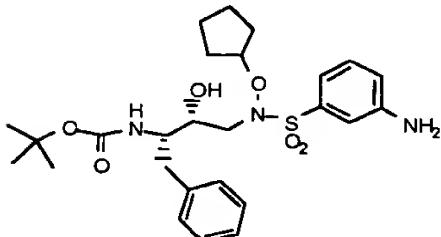
as a solid.  $^1\text{H-NMR}$  (chloroform-D3): 1.71 (m, 8H), 4.71 (m, 1H), 6.93 (bs, 1H), 7.83 (m, 1H), 8.28 (m, 1H), 8.55 (m, 1H), 8.81 (m, 1H).

5 Step 2:



3-amino-N<sup>1</sup>-(cyclopentyloxy)-1-benzenesulfonamide. A solution of  $N^1$ -(cyclopentyloxy)-3-nitro-1-benzenesulfonamide (2.98 g, 10.41 mmol) in 50 mL of absolute ethanol was 10 combined with 5 wt% Palladium on barium sulfate (300 mg) and reduced under a balloon of hydrogen gas with vigorous agitation for 18 hours. The mixture was filtered, washed with ethanol, and evaporated *in vacuo* to a residue. The crude product was purified on flash grade silica gel eluting 15 with 4:1 hexane : ethyl acetate. Fractions containing the product were combined, evaporated *in vacuo* and dried under vacuum to provide 3-amino-N<sup>1</sup>-(cyclopentyloxy)-1-benzenesulfonamide (2.67 g, 100%) as an oil.  $^1\text{H-NMR}$  (chloroform-D3): 1.62 (m, 8H), 3.92 (bs, 2H), 4.58 (m, 1H), 6.74 (bs, 1H), 6.88 (m, 1H), 7.16 (m, 1H), 7.27 (m, 2H). 20  $\text{MS}(\text{ESI})$ : 257 (MH<sup>+</sup>).

Step 3:



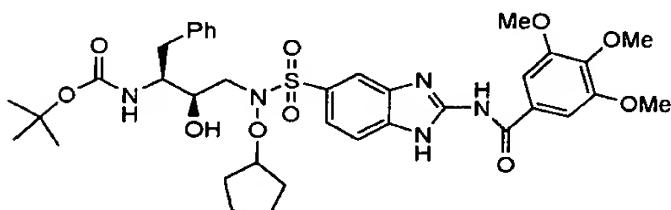
tert-butyl N-(1S,2R)-3-[(3-aminophenyl)sulfonyl](cyclopentyl oxy)amino]-1-benzyl-2-hydroxypropylcarbamate. A solution of 3-amino-N<sup>1</sup>-(cyclopentyloxy)-1-benzenesulfonamide (2.654 g, 10.36 mmol) and tert-butyl N-5 (1S)-1-[(2S)oxiran-2-yl]-2-phenylethylcarbamate (2.181 g, 8.29 mmol) in anhydrous tetrahydrofuran (10 mL) under an Argon atmosphere was treated with phosphazene base P<sub>t</sub>/4-t-Bu (1.60 mL, 1.60 mmol, 1.0 M in hexane). After stirring at ambient temperature for approximately 18 hours, the reaction 10 mixture was quenched with several drops of glacial acetic acid and evaporated *in vacuo*. The residue was partitioned between ethyl acetate and 1N NaHSO<sub>4</sub>. After separating the phases, the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with 15 saturated aqueous brine, dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo* to a residue. The crude product was purified on flash grade silica gel eluting with 95:5 methylene chloride : ethyl acetate (2L); 9:1 methylene chloride : ethyl acetate (2L); and finally 1:1 20 methylene chloride : ethyl acetate. Fractions containing the product were combined, evaporated *in vacuo*, and dried under high vacuum to provide tert-butyl N-(1S,2R)-3-[(3-aminophenyl)sulfonyl](cyclopentyl oxy)amino]-1-benzyl-2-hydroxypropylcarbamate (3.328 g, 77%) as a foam. An 25 analytical sample was obtained by purifying 100 mg on two preparative TLC plate (20x20 cm, 1000  $\mu$ M, silica gel) eluting with 9:1 methylene chloride : methanol. The product bands were removed, eluted with 4:1 methylene chloride : methanol, filtered, and evaporated *in vacuo*. The residue 30 purified again on a preparative TLC plate (20x20 cm, 1000  $\mu$ M, silica gel) eluting with 1:1 ethyl acetate : hexane. The product band was removed, eluted with ethyl acetate, filtered, and evaporated *in vacuo*. The residue was

- 90 -

dissolved in diethylether, evaporated *in vacuo* and dried under high vacuum to provide *tert*-butyl N-(1*S*,2*R*)-3-[(3-aminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate (54 mg) as a foam.  $^1\text{H-NMR}$  (methanol-D<sub>4</sub>): 1.24 (s, 9H), 1.71 (m, 8H), 2.55 (m, 1H), 2.90 (bm, 1H), 3.04 (m, 2H), 3.73 (m, 2H), 4.81 (m, 1H), 6.44 (d, 1H), 6.93 (m, 1H), 7.02 (m, 1H), 7.17 (m, 7H). MS (ESI): 520 (M<sup>+</sup>).

10

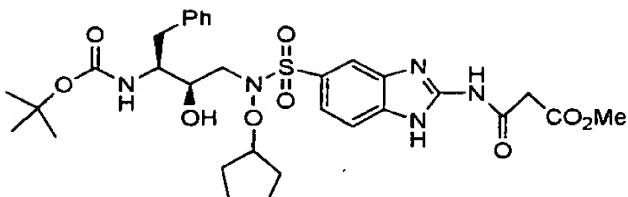
Example 12



(12)

*Tert*-butyl N-(1*S*,2*R*)-1-benzyl-3-[(cyclopentyloxy)(2-[(3,4,5-trimethoxyphenyl-carbonyl)amino]-1*H*-benzimidazol-5-ylsulfonyl)amino]-2-hydroxypropylcarbamate. *Tert*-butyl N-(1*S*,2*R*)-1-benzyl-3-[(cyclopentyloxy)(2-amino-1*H*-benzimidazol-5-ylsulfonyl)amino]-2-hydroxypropylcarbamate (Step 2, Example 8) (130 mg, 0.232 mmol), 3,4,5-trimethoxybenzoyl chloride (70 mg, 0.302 mmol), and anhydrous pyridine (5 mL) were combined in a 25 mL round bottomed flask under nitrogen. The reaction was stirred for 18 hours and then concentrated *in vacuo*. After the workup described in Step 3, Example 54, the residue was purified by preparative silica gel TLC using 90:10 chloroform: methanol as an eluent to give the product as a white film (3 mg, 0.004 mmol).  $^1\text{H-NMR}$  (d<sub>6</sub>-DMSO)  $\delta$ : 7.56-6.63 (m, 7H), 5.21 (bs, 1H), 4.64 (bs, 1H), 3.86 (s, 6H), 3.76 (s, 3H), 3.40-1.30 (m, 18H), 1.23 (s, 9H). MS (ES): 754 (M+1), 752 (M-1).

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Example 13

(13)

5

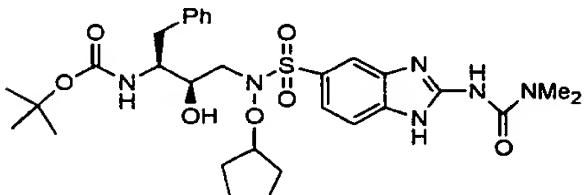
**Tert-butyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)(2-(methyl 3-oxopropionate)amino)-1H-benzimidazol-5-ylsulfonyl]amino]-2-hydroxypropylcarbamate.** Tert-butyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)(2-amino-1H-benzimidazol-5-

10 ylsulfonyl)amino]-2-hydroxypropylcarbamate (Step 2, Example 8) (130 mg, 0.232 mmol), methyl malonyl chloride (0.04 mL, 0.348 mmol), and anhydrous pyridine (5 mL) were combined in a 25 mL round bottomed flask under nitrogen. The reaction was stirred for 18 hours and then concentrated in vacuo.

15 After the workup described in Step 3, Example 54, the residue was purified by preparative silica gel TLC using 90:10 chloroform: methanol as an eluent to give the product

as a pale yellow solid (6 mg, 0.009 mmol). <sup>1</sup>H NMR ( $d_6$ -DMSO)  $\delta$ : 8.62 (d,  $J=8.5$  Hz, 1H), 7.89-6.67 (m, 9H), 5.17 (d,

20  $J=6.0$  Hz, 1H), 4.85 (bs, 1H), 3.65 (s, 3H), 3.77-1.40 (m, 16H), 1.14 (s, 9H). MS(ES): 660 (M+1), 658 (M-1).

Example 14

(14)

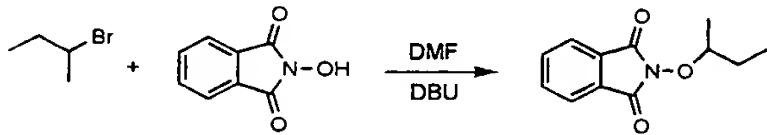
25

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Tert-butyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)(2-[(dimethylamino-carbonyl)amino]-1H-benzimidazol-5-ylsulfonyl)amino]-2-hydroxypropylcarbamate. Tert-butyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)(2-amino-1H-benzimidazol-5-ylsulfonyl)amino]-2-hydroxypropylcarbamate (Step 2, Example 8) (100 mg, 0.179 mmol), dimethyl carbamyl chloride (0.03 mL, 0.286 mmol), and anhydrous pyridine (5 mL) were combined in a 25 mL round bottomed flask under nitrogen. The reaction was stirred for 18 hours and then 10 concentrated in vacuo. After the workup described in Step 3, Example 54, the residue was purified by preparative silica gel TLC using 90:10 chloroform: methanol as an eluent to give the product as a white film (35 mg, 0.056 mmol, 31%).  $^1\text{H}$  NMR ( $\text{d}_6$ -DMSO)  $\delta$ : 7.53-6.66 (m, 8H), 5.10 (bs, 1H), 4.80 (bs, 1H), 3.56 (bs, 2H), 3.20 (s, 3H), 3.18 (s, 3H), 3.10-1.40 (m, 13H), 1.18 (s, 9H). MS (ES): 631 (M+1), 629 (M-1).

Example 15

20 Step 1:

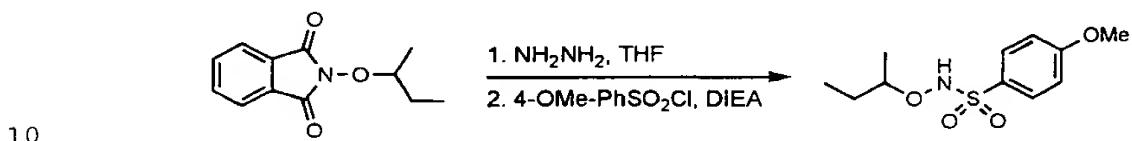


25 2-(sec-butoxy)-1H-isoindole-1,3(2H)-dione.  $N$ -hydroxylphthalimide (18.4 mmol, 3.0 g) was dissolved in anhydrous DMF (20 mL) under nitrogen. To the stirring solution, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) (27.6 mmol, 4.13 mL) was injected followed by 2-bromobutane (22.1 mmol, 2.41 mL) and the reaction was warmed to 55°C. After stirring for 18 hour, the reaction was cooled to room 30 temperature and concentrated to a red oil. The reaction was partitioned between ethyl acetate and 1N HCl. The organic

- 93 -

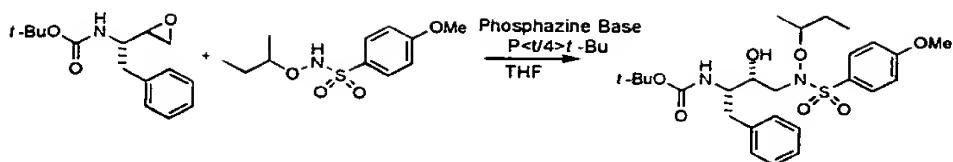
layer was washed with saturated aqueous sodium bicarbonate solution, distilled water, brine and dried over magnesium sulfate. The solvent was removed under vacuum providing 3.57 g (89%) of a yellow solid.  $R_f$ : 0.8 (2:1 hexanes/ethyl acetate);  $H_1$ -NMR ( $CDCl_3$ ):  $\delta$  7.80 (2H, m), 7.73 (2H, m), 4.31 (1H, m), 1.81 (1H, m), 1.64 (1H, m), 1.32 (3H, d), 1.03 (3H, t).

Step 2:



$N^1$ -(sec-butoxy)-4-methoxy-1-benzenesulfonamide.  $O$ -sec-butoxy- $N$ -hydroxylphthalimide (16.3 mmol, 3.57 g) was combined with hydrazine (17.9 mmol, 0.56 mL) in anhydrous THF (30 mL) under nitrogen. The reaction immediately formed a white suspension and was allowed to stir at room temperature for 5 hours. The suspension was filtered directly into a flask containing 4-methoxybenzenesulfonyl chloride (14.6 mmol, 3.03 g) and diisopropylethylamine (17.6 mmol, 3.1 mL) was added. After stirring at room temperature for 15 hours, the reaction was concentrated to a yellow solid and partitioned between ethyl acetate and 1N HCl. The organic layer was separated and washed with a saturated aqueous solution of sodium bicarbonate and brine, and dried over magnesium sulfate. The product was concentrated to a white solid and purified by silica gel chromatography (5:1 hexanes/ethyl acetate), providing 3.13 g (66%) of a white solid.  $H_1$ -NMR ( $CDCl_3$ ):  $\delta$  7.84 (2H, d), 6.98 (2H, d), 6.64 (1H, s), 4.02 (1H, m), 3.86 (3H, s), 1.62-1.55 (1H, m), 1.45-30 1.38 (1H, m), 1.15 (3H, d), 0.87 (3H, t).

## Step 3:



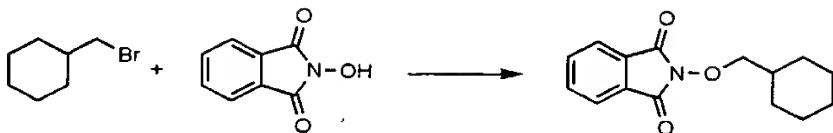
(15)

5 **tert-butyl N-((1S,2R)-1-benzyl-3-sec-butoxy[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate.**  $N^1$ -  
 (sec-butoxy)-4-methoxy-1-benzenesulfonamide (12.1 mmol, 3.13  
 g) was combined with tert-butyl  $N$ -(1S)-1-[(2S)oxiran-2-yl]-  
 10 2-phenylethylcarbamate (13.3 mmol, 3.5 g) and THF (25 mL)  
 under nitrogen. Phosphazine base  $P<t/4>t$ -Bu (2.4 mmol, 2.4  
 mL, 1M in hexanes) was injected into the stirring solution.  
 The reaction was allowed to stir for 48 hours at room  
 temperature and was quenched by the addition of a few drops  
 of glacial acetic acid. The reaction product was  
 15 concentrated to an oil and partitioned between ethyl acetate  
 and 1N HCl. The organic layer was separated and washed with  
 saturated aqueous sodium bicarbonate and brine, dried over  
 magnesium sulfate and concentrated under vacuum to a clear  
 oil. The crude product was purified by silica gel  
 20 chromatography (2:1 hexanes/ethyl acetate) providing 3.03 g  
 (48%) of a white solid.  $H^1$ -NMR ( $CDCl_3$ ):  $\delta$  7.12 (2H, d),  
 7.30-7.19 (6H, m), 6.97 (2H, d), 4.55 (1H, bs), 4.31 (1H, m),  
 3.86 (3H, s), 3.78 (2H, m), 3.5-2.5 (1H, bm), 2.90 (2H, m),  
 1.80-1.60 (1H, m), 1.5-1.3 (1H, m), 1.32 (9H, s), 1.21-1.18  
 25 (3H, m), 0.93-0.85 (3H, m); MS (ESI):  $M+Na = 545$ .

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Example 16

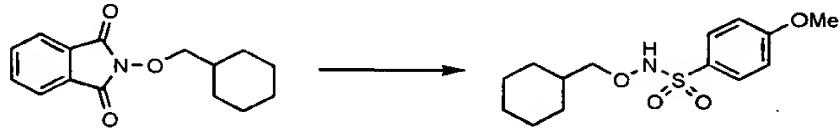
## Step 1:



5

**2-(cyclohexylmethoxy)-1H-isoindole-1,3(2H)-dione.** *N*-hydroxylphthalimide (18.4 mmol, 3.0 g) was dissolved in anhydrous DMF (20 mL) under nitrogen. To the stirring solution, DBU (27.6 mmol, 4.13 mL) was injected followed by cyclohexylmethyl bromide (23.0 mmol, 3.21 mL) and the reaction was warmed to 55°C. After stirring for 15 hours, the reaction was cooled to room temperature and concentrated to a red oil. The reaction was partitioned between ethyl acetate and 1N HCl. The organic layer was washed with saturated aqueous sodium bicarbonate solution, brine and dried over magnesium sulfate. The solvent was removed under vacuum, and the crude product was triturated with hexanes providing 3.05 g (64%) of an off-white colored solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.80 (2H, m), 7.73 (2H, m), 3.98 (2H, d), 2.03-1.65 (5H, m), 1.31-1.03 (6H, m).

## Step 2:

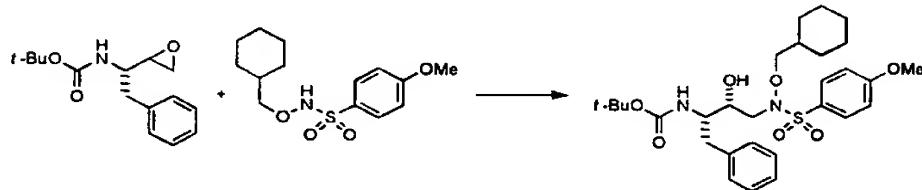


25  **$N^1$ -(cyclohexylmethoxy)-4-methoxy-1-benzenesulfonamide.** 2-(cyclohexylmethoxy)-1H-isoindole-1,3(2H)-dione (11.8 mmol, 3.05 g) was combined with hydrazine (12.9 mmol, 0.41 mL) in anhydrous THF (25 mL) under nitrogen. The reaction immediately formed a white suspension and was allowed to

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stir at room temperature for 48 hours. The suspension was filtered directly into a flask containing 4-methoxybenzenesulfonyl chloride (9.5 mmol, 1.97 g) and diisopropylethylamine (11.6 mmol, 2.03 mL) was added. After 5 stirring at room temperature for 18 hours, the reaction was concentrated to a solid residue and partitioned between ethyl acetate and 1N HCl. The organic layer was separated and washed with a saturated aqueous solution of sodium bicarbonate, and brine, and dried over magnesium sulfate. 10 The product was concentrated to a solid and purified by silica gel chromatography (2:1 hexanes/ethyl acetate) providing 2.55g (80%) of a yellow solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.81 (2H,d), 6.97 (2H,d), 6.78 (1H,s), 3.85 (3H,s), 3.75 (2H,d), 1.65-1.55 (6H,m), 1.25-1.07 (3H,m), 0.93-0.85 15 (2H,m).

Step 3:



(16)

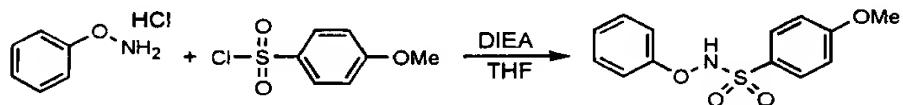
20 **tert-butyl N-((1S,2R)-1-benzyl-3-(cyclohexylmethoxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate.**  $N^1$ -(cyclohexylmethoxy)-4-methoxy-1-benzenesulfonamide (8.52 mmol, 2.55 g) was combined with *tert*-butyl  $N$ -(1*S*)-1-[(2*S*)oxiran-2-yl]-2-phenylethylcarbamate (9.37 mmol, 2.47 g) and THF (16 mL) under nitrogen. Phosphazine base  $P<4>t\text{-Bu}$  (1.7 mmol, 1.7 mL, 1M in hexanes) was injected into the stirring solution. The reaction was allowed to stir for 15 hours at room temperature and was quenched by the addition

of a few drops of glacial acetic acid. The reaction product was concentrated to an oil and partitioned between ethyl acetate and 1N HCl. The organic layer was separated and washed with saturated aqueous sodium bicarbonate and brine, 5 dried over magnesium sulfate and concentrated under vacuum to a clear oil. The crude product was purified by silica gel chromatography (2:1 hexanes/ethyl acetate) providing a white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>):  $\delta$  7.70 (2H, d), 7.28-7.19 (6H, m), 6.97 (2H, d), 4.6 (1H, m), 3.96 (1H, m), 3.87 (3H, s), 10 3.82 (2H, m), 3.21 (1H, m), 2.99 (1H, m), 2.90 (2H, m), 2.80 (1H, m), 1.65 (6H, m), 1.33 (9H, m), 1.2-1.0 (3H, m), 1.00-0.80 (2H, m); MS (ESI): M+Na = 585.

Example 17

15

Step 1:



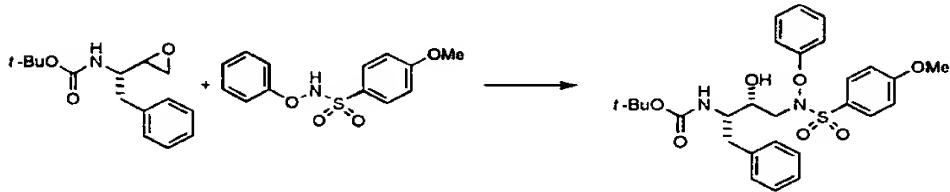
4-methoxy-N<sup>1</sup>-phenoxy-1-benzenesulfonamide. O-

20 phenylhydroxylamine hydrochloride (6.9 mmol, 1.0 g), 4-methoxybenzenesulfonyl chloride (6.2 mmol, 1.29 g), diisopropylethylamine (13.1 mmol, 2.28 mL) and anhydrous THF (15 mL) were combined under nitrogen. After stirring for 2 hours at room temperature, a few crystals of 4-dimethylaminopyridine were added and the flask was re-sealed. After another 2 hours, 4 mL of *N,N*-dimethylformamide was injected and the reaction stirred for an additional 15 hours. The resulting red solution was concentrated to an oil and partitioned between ethyl acetate and 1N HCl. The organic layer was separated and washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated under vacuum. The 25 30

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resulting dark brown residue was purified by silica gel chromatography (3:1 hexanes/ethyl acetate) providing 360 mg (21%) of a reddish solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.89 (2H, d), 7.30-7.20 (3H, m), 7.11 (2H, d), 7.02 (1H, s), 7.00 (2H, d), 5 3.88 (3H, s).

Step 2:



(17)

10

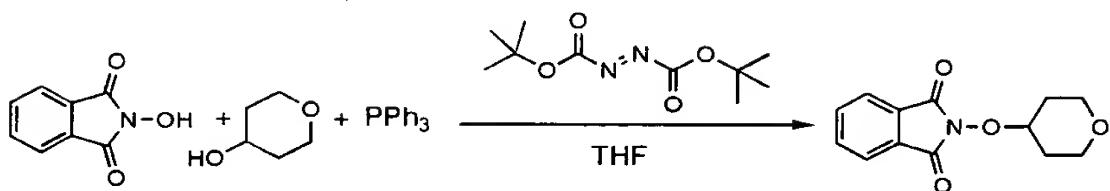
**tert-butyl N-(1S,2R)-1-benzyl-2-hydroxy-3-[(4-methoxyphenyl)sulfonyl] (phenoxy) aminopropylcarbamate.** 4-methoxy- $N^1$ -phenoxy-1-benzenesulfonamide (1.3 mmol, 360 mg) was combined with *tert*-butyl  $N$ -(1S)-1-[(2S)oxiran-2-yl]-2-phenylethylcarbamate (1.4 mmol, 373 mg) and THF (3 mL) under nitrogen. Phosphazine base  $\text{P}(<\text{t}/4>\text{t}-\text{Bu})$  (0.26 mmol, 0.26 mL, 1M in hexanes) was injected into the stirring solution. The reaction was allowed to stir for 48 hours at room temperature and was quenched by the addition of a few drops of glacial acetic acid. The reaction product was concentrated to a red oil and partitioned between ethyl acetate and 1N HCl. The organic layer was separated and washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated under vacuum to a red oil. The crude product was purified by silica gel chromatography (2:1 hexanes/ethyl acetate) and crystallization (hexanes/ethyl acetate) providing 300 mg (43%) of red crystals.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.74 (2H, d), 7.37-7.10 (10H, m), 7.04 (1H, m), 6.98 (2H, d), 4.56 (1H, bs),

- 99 -

3.88 (3H, s), 3.76 (2H, bs), 3.35-3.25 (1H, m), 3.20-2.95 (1H, m), 2.95-2.75 (2H, m), 1.30 (9H, s); MS (ESI): M+Na=565.

Example 18

5 Step 1:



2-(tetrahydro-2H-pyran-4-yloxy)-1H-isoindole-1,3(2H)-dione.

10 A light suspension containing *N*-hydroxylphthalimide (18.4 mmol, 3.0 g), triphenylphosphine (18.4 mmol, 4.82 g), tetrahydro-4H-pyran-4-ol (18.4 mmol, 1.75 mL) and anhydrous THF (50 mL), were transferred to a flask containing di-*tert*-butyl azodicarboxylate (20.2 mmol, 4.66 g) under nitrogen.

15 Over 2 hours the reaction stirred at room temperature and changed from a dark orange to yellow in appearance. The solvent was removed under vacuum and replaced with trifluoroacetic acetic acid (10 mL). The reaction was stirred for 30 minutes and the TFA was removed under vacuum.

20 The crude residue was then dissolved in ethyl acetate, washed with a saturated aqueous solution of sodium bicarbonate, 5% aqueous solution of potassium carbonate, brine and dried over magnesium sulfate. The solvent was removed under vacuum and the residual triphenylphosphine

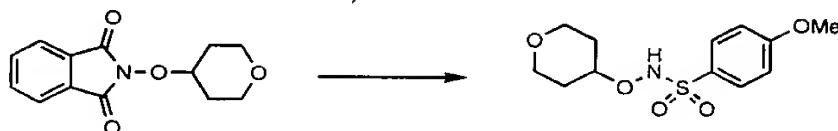
25 oxide was crystallized and filtered using hexanes and ether. The solvent was again removed and the crude solid was purified by silica gel chromatography (2:1 hexanes/ethyl acetate) and recrystallization using methylene chloride and hexanes providing 1.69 g (37%) of a white crystal. R<sub>f</sub> = 0.3

30 (2:1 hexanes/ethyl acetate); H1-NMR (CDCl<sub>3</sub>): δ 7.84-7.82

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(2H, m), 7.75-7.73 (2H, m), 4.46-4.40 (1H, m), 4.08-4.02 (2H, m), 3.50-3.44 (2H, m), 2.04-1.98 (2H, m), 1.92-1.84 (2H, m).

5 Step 2:

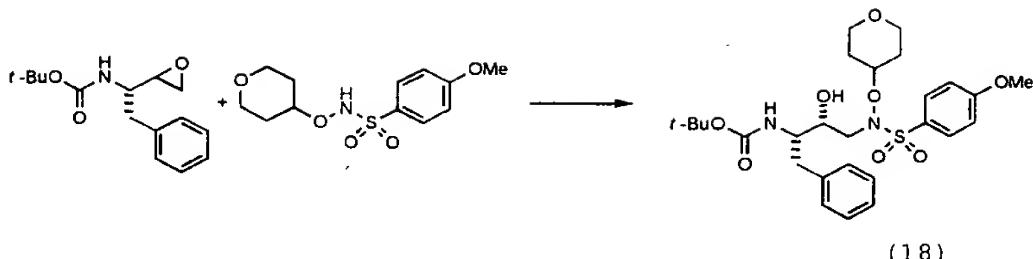


**N-(tetrahydro-2H-pyran-4-yloxy)-4-methoxy-1-**

10 **benzenesulfonamide.** 2-(tetrahydro-2H-pyran-4-yloxy)-1H-isoindole-1,3(2H)-dione (6.8 mmol, 1.69 g) was combined with hydrazine (6.8 mmol, 0.22 mL) in anhydrous THF (20 mL) under nitrogen. The reaction immediately formed a white suspension and was allowed to stir at room temperature for 1 hour. The suspension was filtered directly into a flask containing 4-methoxybenzenesulfonyl chloride (6.5 mmol, 1.34 g) and diisopropylethylamine (20.5 mmol, 3.6 mL) was added. After stirring at room temperature for 15 hours, the reaction was refluxed for 4 hours, then stirred at room temperature for 12 days and concentrated to a yellow solid. The resulting solid was partitioned between ethyl acetate and 1N HCl, and the organic layer was separated and washed with a saturated aqueous solution of sodium bicarbonate and brine, and dried over magnesium sulfate. The crude product was concentrated to a white solid and purified by silica gel chromatography (1:1 hexanes/ethyl acetate) and crystallization (hexanes/ethyl acetate) providing 0.554 g (30%) of a white solid.  $R_f$  = 0.4 (1:1 hexanes/ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.83 (2H, d), 7.00 (2H, d), 6.72 (1H, s), 4.23-4.11 (1H, m), 3.91-3.81 (2H, m), 3.87 (3H, s), 3.46-3.38 (2H, m), 2.03-1.94 (2H, m), 1.63-1.51 (2H, m).

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Step 3:



5

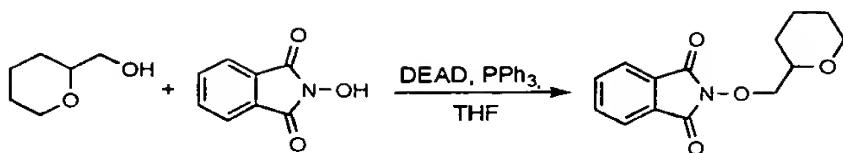
**tert-butyl N-(1S,2R)-1-benzyl-2-hydroxy-3-[(4-methoxyphenyl)sulfonyl](tetrahydro-2H-pyran-4-yloxy)amino]propylcarbamate.** *N*-(tetrahydro-2H-pyran-4-yloxy)-4-methoxy-1-benzenesulfonamide (1.93 mmol, 554 mg)

10 was combined with *tert*-butyl *N*-(1*S*)-1-[(2*S*)oxiran-2-yl]-2-phenylethylcarbamate (1.54 mmol, 406 mg) and THF (5 mL) under nitrogen. Phosphazine base P<sub>t</sub>-*t*-Bu (0.31 mmol, 0.31 mL, 1M in hexanes) was injected into the stirring solution. The reaction was allowed to stir for 15 hours at 15 room temperature, quenched by the addition of a few drops of glacial acetic acid and concentrated. The organic layer was separated and washed with 1N NaOH, dried over magnesium sulfate and concentrated under vacuum. The crude product was purified by silica gel chromatography (2:1 hexanes/ethyl 20 acetate) and crystallization (hexanes/ethyl acetate) providing 367 mg (43%) of a white crystal. *R*<sub>f</sub> = 0.2 (8:1 CH<sub>2</sub>Cl<sub>2</sub>/ethyl acetate); *H*1-NMR (CDCl<sub>3</sub>): δ 7.70 (2H, d), 7.30-7.18 (6H, m), 6.97 (2H, d), 4.60-4.51 (1H, m), 4.44-4.33 (2H, m), 3.97-3.88 (2H, m), 3.86 (3H, s), 3.83-3.71 (2H, m), 25 3.48-3.34 (2H, m), 3.40-2.60 (1H, bs), 2.95-2.85 (2H, m), 2.07-1.95 (2H, m), 1.56-1.49 (2H, m), 1.32 (9H, s); MS (ESI): M+Na=573.

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Example 19

Step 1:



5 **2-(tetrahydro-2H-pyran-2-ylmethoxy)-1H-isoindole-1,3(2H)-dione.** This reaction was conducted according to the procedure reported in Grochowski, E; Jurczak, J. *Synthesis* 1976, 682.  $R_f$  = 0.3 (2:1 hexanes/ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.83-7.79 (2H, m), 7.75-7.70 (2H, m), 4.24-4.18 (1H, m), 4.07-4.03 (1H, m), 3.94-3.89 (1H, m), 3.81-3.75 (1H, m), 3.46-3.37 (1H, m), 1.87-1.85 (1H, m), 1.63-1.33 (5H, m).

10

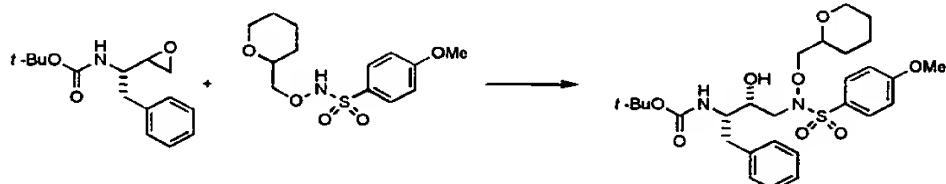
Step 2:



15 ***N*-(tetrahydro-2H-pyran-2-ylmethoxy)-4-methoxy-1-benzenesulfonamide.** 2-(tetrahydro-2H-pyran-2-ylmethoxy)-1H-isoindole-1,3(2H)-dione (6.8 mmol, 1.77 g) was combined with hydrazine (6.8 mmol, 0.21 mL) in anhydrous THF (15 mL) under nitrogen. The reaction immediately formed a white suspension and was allowed to stir at room temperature for 2 hours. The suspension was filtered directly into a flask containing 4-methoxybenzenesulfonyl chloride (6.8 mmol, 1.40 g) and diisopropylethylamine (8.1 mmol, 1.42 mL) was added. After stirring at room temperature for 24 hours, the reaction was concentrated to a yellow solid. The resulting solid was partitioned between ethyl acetate and 1N HCl, and

the organic layer was separated and washed with a saturated aqueous solution of sodium bicarbonate and brine, and dried over magnesium sulfate. The crude product was concentrated to a yellow solid and purified by silica gel chromatography 5 (2:1 hexanes/ethyl acetate). The purified product was combined with ether and filtered to remove the residual phthalimide-hydrazine biproduct. The final product was crystallized using hexanes and ethyl acetate to provide 141 mg (7%) of white crystals.  $R_f$  = 0.3 (2:1 hexanes/ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.83 (2H, d), 7.05 (1H, s), 6.97 (2H, d), 4.01-3.86 (3H, m), 3.86 (3H, s), 3.63-3.57 (1H, m), 3.42-3.36 (1H, m), 1.88-1.78 (1H, m), 1.59-1.43 (4H, m), 1.3-1.15 (1H, m).

## 15 Step 3:



(19)

20 **tert-butyl N-(1S,2R)-1-benzyl-2-hydroxy-3-[(4-methoxyphenyl)sulfonyl](tetrahydro-2H-pyran-2-ylmethoxy)amino]propylcarbamate.**  $N$ -(tetrahydro-2H-pyran-2-ylmethoxy)-4-methoxy-1-benzenesulfonamide (0.47 mmol, 141 mg) was combined with *tert*-butyl  $N$ -(1S)-1-[(2S)oxiran-2-yl]-2-phenylethylcarbamate (0.37 mmol, 99 mg) and THF (1 mL) 25 under nitrogen. Phosphazine base  $P< t/4>t\text{-Bu}$  (0.08 mmol, 0.08 mL, 1M in hexanes) was injected into the stirring solution. The reaction was allowed to stir for 15 hours at room temperature, quenched by the addition of a few drops of glacial acetic acid and concentrated. The crude residue was

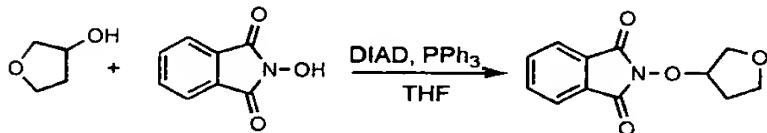
- 104 -

partitioned between ethyl acetate and 1N HCl, and the organic layer was separated and washed with saturated aqueous sodium bicarbonate solution and brine, and dried over magnesium sulfate. The crude product was purified by 5 silica gel chromatography (2:1 hexanes/ethyl acetate). The purified product was then washed with 1N NaOH to remove remaining sulfonamide starting material that coeluted, brine, and was again dried over magnesium sulfate. The silica gel chromatography was repeated and yielded 130 mg 10 (62%) of a white solid.  $R_f$  = 0.2 (2:1 hexanes/ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.68-7.64 (2H, m), 7.28-7.18 (6H, m), 6.96 (2H, d), 4.74-4.60 (1H, m), 4.37-4.18 (1H, m), 4.14-4.06 (1H, m), 4.01-3.93 (2H, m), 3.90-3.75 (2H, m), 3.87 (3H, s), 3.66-3.46 (1H, m), 3.46-3.35 (1H, m), 2.92-2.74 15 (2H, m), 3.50-2.50 (1H, bs), 1.90-1.81 (1H, m), 1.63-1.42 (4H, m), 1.34 (9H, s), 1.29-1.20 (1H, m);  $\text{MS}$  (ESI):  $M=565$ .

Example 20

Step 1:

20

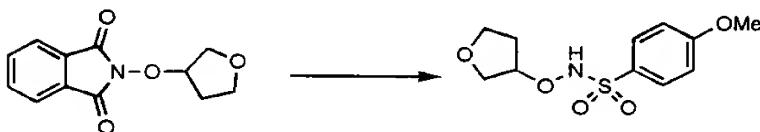


2-(tetrahydro-3-furanyloxy)-1H-isoindole-1,3(2H)-dione. To a light suspension containing *N*-hydroxylphthalimide (5.7 25 mmol, 926 mg), triphenylphosphine (5.7 mmol, 1.49 g), tetrahydro-4H-furan-3-ol (5.7 mmol, 0.459 mL) and anhydrous THF (10 mL), diisopropylazodicarboxylate (6.2 mmol, 1.23 mL) was injected under nitrogen atmosphere. The reaction 30 stirred at room temperature for 5 hours and changed from a dark orange to yellow in appearance. The solvent was removed under vacuum, and the resulting residue was purified

- 105 -

by silica gel chromatography (2:1 hexanes/ethyl acetate) and crystallization (hexanes/ethyl acetate) providing 373 mg (28%) of white crystals.  $R_f$  = 0.5 (1:1 hexanes/ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.85-7.82 (2H, m), 7.77-7.74 (2H, m), 5.05 (1H, m), 4.16-4.09 (2H, m), 3.92-3.87 (2H, m), 2.34-2.28 (1H, m), 2.11-2.03 (1H, m).

Step 2:



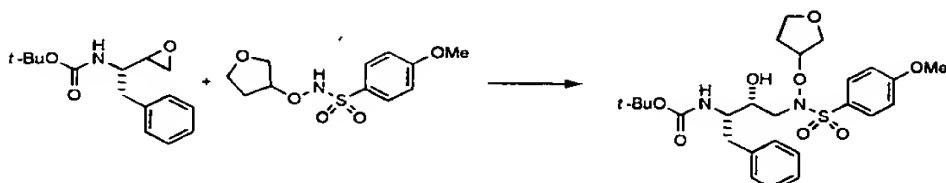
10

***N-(tetrahydro-3-furanyloxy)-4-methoxy-1-benzenesulfonamide.*** 2-(tetrahydro-3-furanyloxy)-1*H*-isoindole-1,3(2*H*)-dione (1.5 mmol, 357 mg) was combined with hydrazine (1.7 mmol, 0.053 mL) in anhydrous THF (3 mL) under nitrogen. The reaction 15 immediately formed a white suspension and was allowed to stir at room temperature for 1 hour. The suspension was filtered directly into a flask containing 4-methoxybenzenesulfonyl chloride (1.5 mmol, 316 mg) and diisopropylethylamine (1.8 mmol, 0.320 mL) was added. After 20 stirring at room temperature for 18 hours, the reaction was concentrated to a solid. The resulting solid was partitioned between ethyl acetate and 1N HCl, and the organic layer was separated and washed with a saturated aqueous solution of sodium bicarbonate and brine, and dried over magnesium 25 sulfate. The crude product was concentrated to a white solid and purified by silica gel chromatography (1:1 hexanes/ethyl acetate). The purified product was then combined with ether and filtered to remove the residual phthalimide-hydrazine biproduct. The filtrate was then 30 crystallized by adding hexanes providing 203 mg (48%) white crystals.  $R_f$  = 0.2 (1:1 hexanes/ethyl acetate);  $^1\text{H-NMR}$

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(CDCl<sub>3</sub>): δ 7.82 (2H, d), 6.99 (2H, d), 6.85 (1H, s), 4.82-4.79 (1H, m), 3.97-3.87 (2H, m), 3.87 (3H, s), 3.83-3.70 (2H, m), 2.12-1.99 (2H, m).

5 Step 3:



(20)

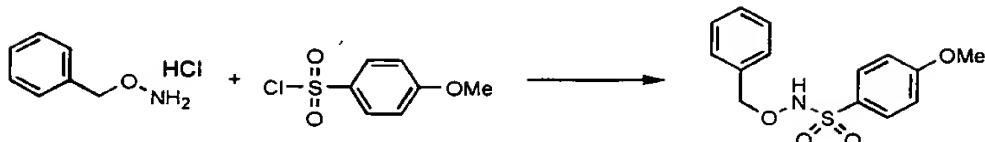
10 **tert-butyl N-(1S,2R)-1-benzyl-2-hydroxy-3-[(4-methoxyphenyl)sulfonyl](tetrahydro-3-furanyloxy)amino]propylcarbamate.** N-(tetrahydro-3-furanyloxy)-4-methoxy-1-benzenesulfonamide (1.03 mmol, 283 mg) was combined with *tert*-butyl N-(1*S*)-1-[(2*S*)oxiran-2-yl]-2-phenylethylcarbamate (1.35 mmol, 300 mg) and THF (1 mL) under nitrogen. Phosphazine base P<4>-*t*-Bu (0.21 mmol, 0.21 mL, 1M in hexanes) was injected into the stirring solution. The reaction was allowed to stir for 15 hours at room temperature, quenched by the addition of a few drops of glacial acetic acid and concentrated. The crude residue was partitioned between ethyl acetate and 1N HCl, and the organic layer was separated and washed with saturated aqueous sodium bicarbonate solution and brine, and dried over magnesium sulfate. The crude product was purified by silica gel chromatography (2:1 hexanes/ethyl acetate) and reverse phase HPLC (water/acetonitrile) yielding 60 mg (11%) of a white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.68 (2H, d), 7.32-7.13 (6H, m), 7.01-6.93 (2H, m), 5.17-5.00 (1H, m), 4.66-4.51 (1H, m), 4.34-4.16 (1H, m), 3.87 (3H, s), 3.83-3.68 (5H, m),

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3.67-3.57 (1H, m), 2.95-2.78 (2H, m), 2.70 (1H, bs), 2.18-1.97 (2H, m), 1.34 (9H, m); MS (ESI): M+Na=559.

Example 21

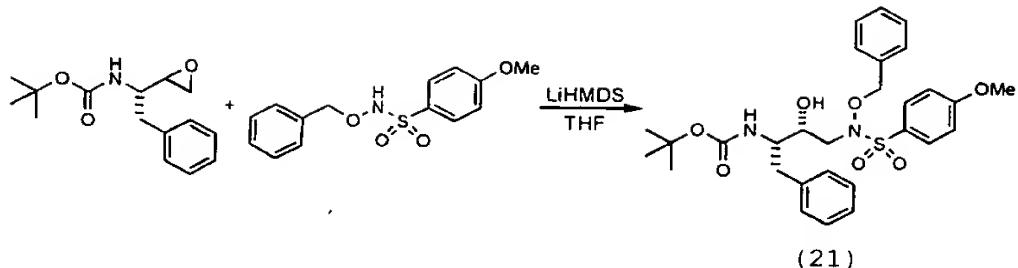
5 Step 1:



**N<sup>1</sup>-(benzyloxy)-4-methoxy-1-benzenesulfonamide.** O-  
 Benzylhydroxylamine hydrochloride (31.3 mmol, 5.0 g), 4-  
 10 methoxybenzenesulfonyl chloride (34.5 mmol, 7.12 g) and  
 anhydrous THF (50 mL) were combined under nitrogen. The  
 reaction was cooled to 0°C and diisopropylethylamine (69.0  
 mmol, 12.0 mL) was injected. The reaction was allowed to  
 warm to room temperature and continued to stir for 18 hours.  
 15 An additional 0.25 equivalents of O-Benzylhydroxylamine  
 hydrogen chloride (7.8 mmol, 1.25 g) and 0.75 equivalents of  
 diisopropylethylamine (23.5 mmol, 4.1 mL) were added to  
 encourage complete conversion of the remaining sulfonyl  
 chloride. The reaction stirred for 4 additional hours at  
 20 room temperature. The reaction solution was concentrated to  
 a solid and partitioned between ethyl acetate and 1N HCl.  
 The organic layer was dried over magnesium sulfate and  
 concentrated under vacuum to yield 9.83 g (76%) of an off-  
 white colored solid. R<sub>f</sub>: 0.2 (2:1 hexanes/ethyl acetate);  
 25 H<sub>1</sub>-NMR (CDCl<sub>3</sub>): δ 7.84 (2H, d), 7.34 (5H, s) 7.08 (2H, d),  
 4.92 (2H, s), 3.88 (3H, s).

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Step 2:

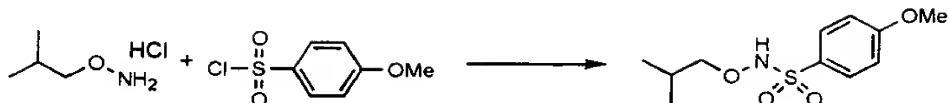


5 **tert-butyl N-((1S,2R)-1-benzyl-3-(benzyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate.** Lithium hexamethyldisilazide (0.6 mmol, 0.6 mL, 1M in THF) was injected into a stirring solution of  $N^1$ -(benzyloxy)-4-methoxy-1-benzenesulfonamide (3.0 mmol, 1.0 g), tert-butyl 10  $N$ -(1S)-1-[(2S)oxiran-2-yl]-2-phenylethylcarbamate (2.4 mmol, 0.64 g), and anhydrous THF (8 mL). The reaction was allowed to stir for 15 hours at room temperature under nitrogen. The reaction was quenched with a few drops of glacial acetic acid and concentrated to a thick oil. The crude was 15 partitioned between ethyl acetate and 1N HCl, washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated. The crude product was purified by silica gel chromatography (2:1 hexanes/ethyl acetate) and crystallized from ethyl acetate with hexanes, 20 providing 400 mg (22%) of a white crystal.  $R_f$ : 0.4 (2:1 hexanes/ethyl acetate);  $H^1$ -NMR ( $CDCl_3$ ):  $\delta$  7.72 (2H, d), 7.4-7.3 (5H, m), 7.3-7.2 (5H, m), 7.19 (1H, d), 6.93 (2H, d), 5.08 (2H, s), 4.40 (1H, m), 3.82 (3H, s), 3.69 (1H, m), 3.53 (1H, bs), 2.98 (1H, bs), 2.83 (2H, m), 2.71 (1H, bs), 1.33 (9H, s); MS 25 (ESI):  $M+Na$  = 579.

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Example 22

Step 1:

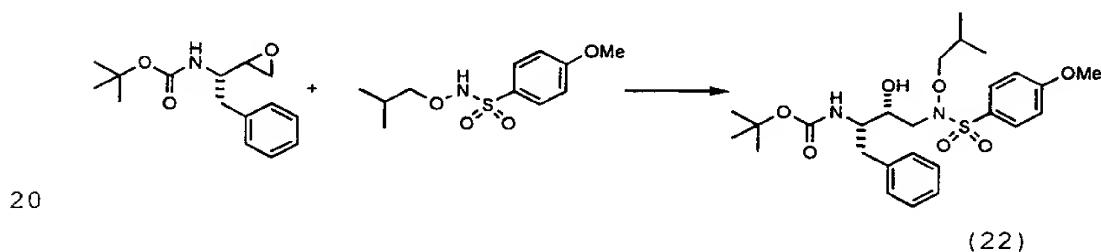


5 **N<sup>1</sup>-isobutoxy-4-methoxy-1-benzenesulfonamide.** Isobutoxyamine hydrochloride (7.96 mmol, 1.0 g), 4-methoxybenzenesulfonyl chloride (7.24 mmol, 1.5 g), diisopropylethylamine (18.09 mmol, 3.15 mL) and anhydrous THF (15 mL) were combined under nitrogen. The reaction stirred at room temperature for 15 hours. The reaction solution was concentrated to a white solid and partitioned between ethyl acetate and 1N HCl. The organic layer was separated and washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate and concentrated under vacuum to yield an off-white colored solid.  $R_f$ : 0.5 (2:1 hexanes/ethyl acetate); H<sub>1</sub>-NMR (CDCl<sub>3</sub>):  $\delta$  7.84 (2H, d), 6.99 (2H, d), 6.81 (1H, s), 3.87 (3H, s), 3.74 (2H, d), 1.90 (1H, septet), 0.86 (6H, d).

10

15

Step 2:



25 **tert-butyl N-((1S,2R)-1-benzyl-2-hydroxy-3-isobutoxy[(4-methoxyphenyl) sulfonyl] aminopropyl)carbamate.** Synthesized under the same conditions as outlined for **tert-butyl N-((1S,2R)-1-benzyl-3-(benzyloxy)[(4-methoxyphenyl) sulfonyl] amino-2-hydroxypropyl)carbamate 21.** H<sub>1</sub>-NMR (CDCl<sub>3</sub>):  $\delta$  7.70

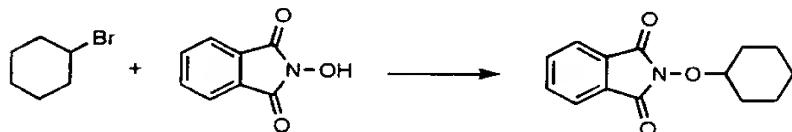
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(2H, d), 7.30-7.10 (6H, m), 6.96 (2H, d), 4.60 (1H, m), 3.93 (1H, m), 3.86 (3H, s), 3.81 (2H, m), 3.24 (1H, m), 3.01 (1H, m), 2.90 (2H, m), 2.82 (1H, m), 1.82 (1H, septet), 1.32 (9H, s), 0.93-0.81 (6H, m); MS (ESI): M+Na = 545.

5

Example 23

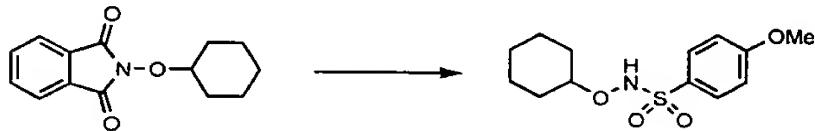
Step 1:



10 2-(cyclohexyloxy)-1*H*-isoindole-1,3(2*H*)-dione. *N*-hydroxylphthalimide (61.3 mmol, 10.0 g) was dissolved in anhydrous DMF (60 mL) under nitrogen. To the stirring solution, DBU (92.0 mmol, 13.75 mL) was injected followed by cyclohexyl bromide (76.6 mmol, 9.43 mL) and the reaction was 15 warmed to 55°C. After stirring for 15 hours, the reaction was warmed to 80°C for 5 hours, then cooled to room temperature and concentrated to a red oil. The reaction was partitioned between ethyl acetate and 1N HCl. The organic layer was washed with 1N NaOH, brine and dried over 20 magnesium sulfate. The solvent was removed under vacuum and the crude product was triturated with hexanes providing 2.89 g (19%) of a yellow solid. R<sub>f</sub>: 0.7 (2:1 hexanes/ethyl acetate); <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.80 (2H, m), 7.73 (2H, m), 4.21 (1H, m), 2.02-1.98 (2H, m), 1.87-1.82 (2H, m), 1.59-1.53 (4H, m), 1.30-1.24 (2H, m).

25

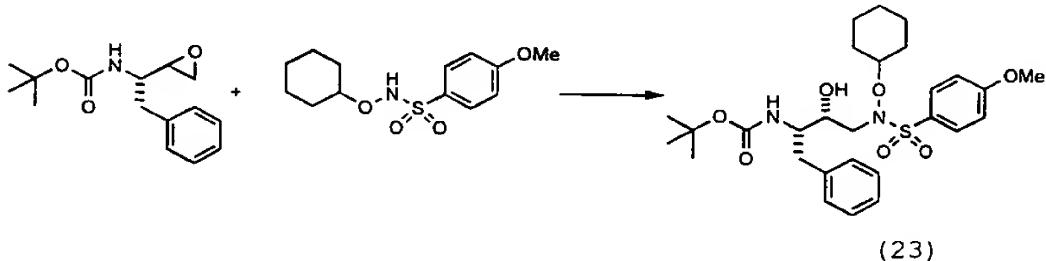
Step 2:



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***N<sup>1</sup>-(cyclohexyloxy)-4-methoxy-1-benzenesulfonamide.*** 2-(cyclohexyloxy)-1*H*-isoindole-1,3(2*H*)-dione (11.8 mmol, 2.89 g) was combined with hydrazine (13.0 mmol, 0.41 mL) in anhydrous THF (20 mL) under nitrogen. The reaction 5 immediately formed a white suspension and was allowed to stir at room temperature for 18 hours. The suspension was filtered directly into a flask containing 4-methoxybenzenesulfonyl chloride (10.6 mmol, 2.20 g) and diisopropylethylamine (14.2 mmol, 2.47 mL) was added. After 10 stirring at room temperature for 24 hours, the reaction was concentrated to a yellow solid and partitioned between ethyl acetate and 1N HCl. The organic layer was separated and washed with a saturated aqueous solution of sodium bicarbonate, and brine, and dried over magnesium sulfate. 15 The product was concentrated to a yellow solid and purified by silica gel chromatography (1:1 hexanes/ethyl acetate) providing 2.53 g (83%) of a white solid.  $R_f$ : 0.2 (2:1 hexanes/ethyl acetate);  $^1$ H-NMR ( $CDCl_3$ ):  $\delta$  7.86 (2H, d), 7.00 (2H, d), 6.67 (1H, s), 3.98-3.95 (1H, m), 3.88 (3H, s), 2.00-20 1.94 (2H, m), 1.75-1.55 (2H, m), 1.35-1.17 (6H, m).

Step 3:



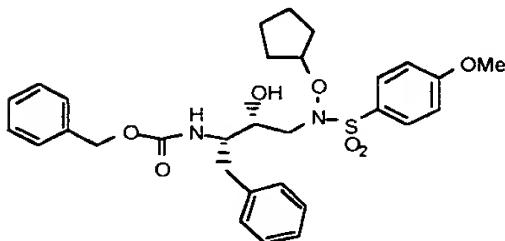
25

***tert-butyl N-((1S,2R)-1-benzyl-3-(cyclohexyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate.*** Synthesized under the same conditions as outlined for *tert-butyl N-((1S,2R)-1-benzyl-3-(benzyloxy)[(4-methoxyphenyl)*

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sulfonyl] amino-2-hydroxypropyl) carbamate.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.77 (2H, d), 7.33-7.25 (6H, m), 7.02 (2H, d), 4.60 (1H, m), 4.24 (1H, m), 3.87 (3H, s), 3.84 (3H, m), 3.5-2.5 (1H, m), 2.96 (2H, m), 2.09 (2H, m), 1.77 (2H, m), 1.38 (9H, s), 1.2-1.0 (6H, m);  $\text{MS}$  (APCI):  $\text{M}+\text{Na} = 571$ .

Example 24



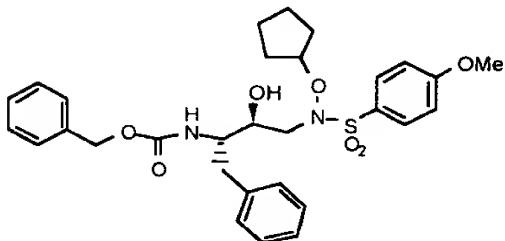
10 (24)

**Phenylmethyl  $N$ -((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)-[4-methoxyphenyl]sulfonyl)amino-2-hydroxypropyl) carbamate.** To a solution of  $N^1$ -[(2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl]- $N^2$ -(cyclopentyloxy)-4-methoxy-1-benzenesulfonamide x trifluoracetic acid (Step 1, Example 48), (50 mg, 0.091 mmol) in approximately 1.5 mL of dichloromethane under Argon was added benzylchloroformate (15.6  $\mu\text{L}$ , 0.109 mmol) followed by *N,N*-diisopropylethylamine (47.9  $\mu\text{L}$ , 0.273 mmol). After stirring 18 hours, the reaction mixture was evaporated *in vacuo* to a residue and purified on a preparative silica gel TLC plate (20x20 cm, 1000  $\mu\text{M}$ ) eluting with 95:5 methylene chloride : methanol. The product band was removed, eluted with 4:1 methylene chloride : methanol, filtered, and evaporated *in vacuo*. The residue was partitioned between dichloromethane and water. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and

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evaporated *in vacuo*. The residue was lyophilized from acetonitrile and water to provide phenylmethyl *N*-(*(1S,2R)*-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate (37 mg, 71%). <sup>1</sup>H-NMR (methanol-D<sub>4</sub>) 5 1.71 (m, 8H), 2.59 (m, 1H), 2.93 (m, 2H), 3.10 (m, 1H), 3.81 (m, 2H), 3.83 (s, 3H), 4.86 (m, 3H), 7.06 (m, 2H), 7.21 (m, 10H), 7.73 (m, 2H). MS(ESI): 591 (M+Na).

An isomer of Compound 24, with inverted stereochemistry at 10 C-2 was prepared as follows:

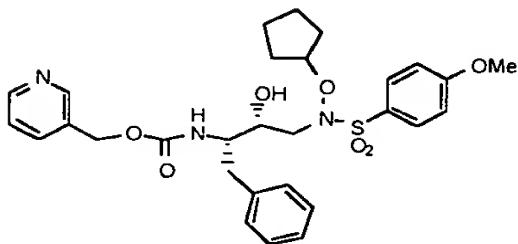


**Phenylmethyl *N*-(*(1S,2S)*-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate.** A 15 mixture of phenylmethyl *N*-(*1S*)-1-[(*2S*)oxiran-2-yl]-2-phenylethylcarbamate [250 mg, 0.842 mmol, Tetrahedron (1994), 50(21), 6333-46] and *N*<sup>1</sup>-(cyclopentyloxy)-4-methoxy-1-benzenesulfonamide (285 mg, 1.05 mmol) in anhydrous tetrahydrofuran (3 mL) under an Argon atmosphere was treated 20 with phosphazene base P<*t*/4>*t*-Bu (0.168 mL, 0.168 mmol, 1.0 M in hexane). The mixture was stirred at ambient temperature for approximately 18 hours, quenched with several drops of glacial acetic acid and evaporated *in vacuo*. The residue was purified on flash grade silica gel 25 eluting with 4:1 hexane : ethyl acetate. Fractions containing the product were combined and evaporated *in vacuo*. The residue was triturated with hexane and then evaporated *in vacuo* and dried under high vacuum to provide

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phenylmethyl *N*-((1*S*,2*S*)-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate (439 mg, 92%) as a foam. *H*1-NMR (methanol-D4) 1.66 (m, 8H), 2.94 (m, 4H), 3.83 (m, 2H), 3.92 (s, 3H), 4.59 (m, 1H), 5.10 (m, 2H), 7.10 (m, 2H), 7.29 (m, 10H), 7.69 (m, 2H). MS(ESI): 591 (M+Na).

Example 25



10 (25)

3-pyridylmethyl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate.

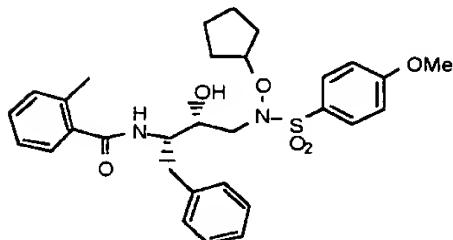
Carbonyldiimidazole (13.0 mg, 0.080 mmol) and 3-15 hydroxymethylpyridine (7.8  $\mu$ L, 0.080 mmol) were combined under an Argon atmosphere in 2.5 mL of anhydrous ethyl acetate. After stirring for 1.5 hours at ambient temperature, *N*<sup>1</sup>-[(2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl]-*N*<sup>2</sup>-(cyclopentyloxy)-4-methoxy-1-benzenesulfonamide x 20 trifluoracetic acid (Step 1, Example 48), (40 mg, 0.073 mmol) was added and the mixture was heated at reflux for 5 hours. Heating was discontinued and the solvent was removed under vacuum. The crude product was purified on a preparative TLC plate (20x20 cm, 1000  $\mu$ M) eluting with 93:7 25 methylene chloride : methanol. The product band was removed, eluted with 3:1 methylene chloride : methanol, filtered, and evaporated *in vacuo*. The residue was dissolved in diethylether, evaporated *in vacuo* and dried.

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under high vacuum to provide 3-pyridylmethyl *N*-(*(1S,2R)*-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate (18.9 mg, 41%) as a foam.  $^1\text{H}$ -NMR (chloroform-D3): 1.66 (m, 8H), 2.95 (m, 5H), 3.86 (s, 3H), 5 3.87 (m, 2H), 4.77 (m, 1H), 4.98 (m, 3H), 6.97 (d, 2H), 7.20 (m, 6H), 7.54 (m, 1H), 7.68 (d, 2H), 8.54 (bm, 2H).  
MS (ESI): 570 (MH $^+$ ).

Example 26

10



(26)

*N*<sup>1</sup>-*((1S,2R)*-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)-2-methylbenzamide.

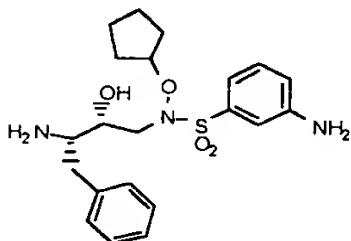
15 Toluoyl chloride (7.8  $\mu\text{L}$ , 0.0602 mmol) was added to a solution of *N*<sup>1</sup>-*((2R,3S)*-3-amino-2-hydroxy-4-phenylbutyl)-*N*<sup>1</sup>-(cyclopentyloxy)-4-methoxy-1-benzenesulfonamide x  
trifluoracetic acid (Step 1, Example 48), (30 mg, 0.055  
mmol) and *N,N*-diisopropylethylamine (23.8  $\mu\text{L}$ , 0.137 mmol) in  
20 approximately 1.5 mL of dichloromethane under Argon. After  
stirring for 18 hours at ambient temperature, the reaction  
solvent was removed *in vacuo* and the residue was purified on  
a preparative TLC plate (20x20 cm, 500  $\mu\text{M}$ ) eluting with 96:4  
methylene chloride : methanol. The product band was  
25 removed, eluted with 4:1 methylene chloride : methanol,  
filtered, and evaporated *in vacuo*. The residue was  
triturated from diethylether and hexane and the solvents  
were evaporated *in vacuo* to provide *N*<sup>1</sup>-*((1S,2R)*-1-benzyl-3-

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(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)-2-methylbenzamide (27 mg, 89%) as a solid. H1-NMR (dimethylsulfoxide-D6): 1.75 (m, 8H), 1.87 (s, 3H), 2.63 (m, 1H), 2.79 (bm, 1H), 3.05 (bm, 1H), 3.21 (bm, 1H), 5 3.69 (bm, 1H), 3.86 (s, 3H), 4.13 (bm, 1H), 4.86 (bm, 1H), 5.28 (bs, 1H), 6.79 (m, 1H), 7.21 (m, 10H), 7.72 (d, 2H), 8.06 (d, 1H). MS (ESI): 575 (M+Na).

Example 27

10 Step 1:

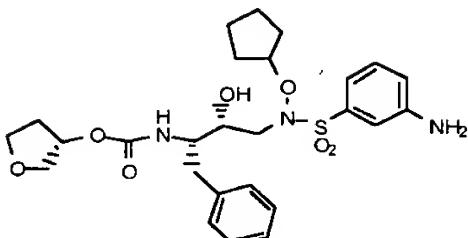


3-amino- $N^1$ -[(2R,3S)-3-amino-2-hydroxy-4-phenylbutyl]- $N^1$ - (cyclopentyloxy)-1-benzenesulfonamide. A mixture of N-15 (1S,2R)-3-[(3-aminophenyl)sulfonyl](cyclopentyloxy)amino)-1-benzyl-2-hydroxypropylcarbamate (Step 3, Example 11), (1.500 g, 2.89 mmol) and trifluoroacetic acid (5 mL) was stirred under an Argon atmosphere at ambient temperature for 30 minutes. Trifluoroacetic acid was removed *in vacuo* and 20 the residue was partitioned between dichloromethane and 1N NaOH. After separating the phases, the aqueous layer was extracted twice with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate, filtered, evaporated *in vacuo* and dried under high vacuum to provide 25 3-amino- $N^1$ -[(2R,3S)-3-amino-2-hydroxy-4-phenylbutyl]- $N^1$ - (cyclopentyloxy)-1-benzenesulfonamide (1.157 g, 96%) as a foam. H1-NMR (methanol-D4): 1.68 (m, 8H), 2.55 (m, 1H), 2.79 (m, 1H), 2.94 (bm, 1H), 3.12 (m, 2H), 3.77 (m, 1H),

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4.76 (m, 1H), 6.96 (m, 1H), 7.05 (m, 1H), 7.16 (m, 4H), 7.27 (m, 3H). MS (ESI): 420 (MH<sup>+</sup>).

Step 2:



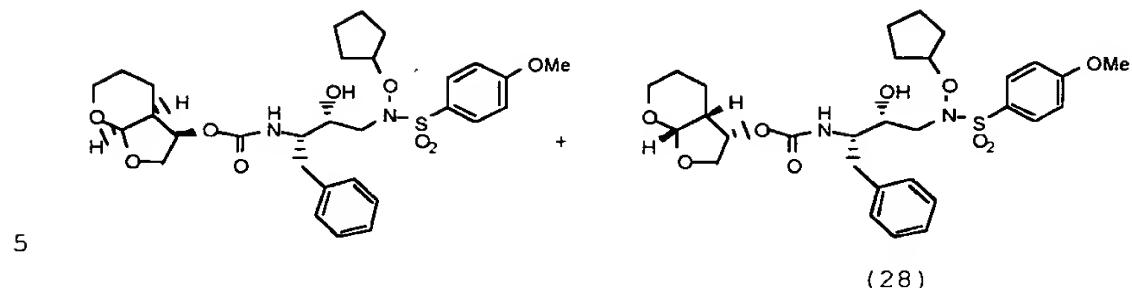
(27)

(3*S*) tetrahydro-3-furanyl *N*-(1*S*,2*R*)-3-[(3-aminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate. A mixture of 3-amino-*N*<sup>1</sup>-[(2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl]-*N*<sup>1</sup>-(cyclopentyloxy)-1-benzenesulfonamide (100 mg, 0.239 mmol), 2,5-dioxo-1-pyrrolidinyl [(3*S*) tetrahydro-3-furanyl] carbonate (55 mg, 0.239 mmol, WO94/05639) and *N,N*-diisopropylethylamine (41.6  $\mu$ L, 0.239 mmol) were combined under Argon at ambient temperature in approximately 1.5 mL of acetonitrile. After stirring for approximately 18 hours, the reaction mixture was evaporated *in vacuo* and purified on two preparative silica gel TLC plates (20x20 cm, 1000  $\mu$ M) eluting with 95:5 methylene chloride methanol. The product band was removed, eluted with 3:1 methylene chloride : methanol, filtered, evaporated *in vacuo* and dried under high vacuum to provide (3*S*) tetrahydro-3-furanyl *N*-(1*S*,2*R*)-3-[(3-aminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate (111 mg, 87%) as a foam. *H*<sub>1</sub>-NMR (methanol-D<sub>4</sub>): 1.80 (m, 9H), 2.61 (m, 1H), 3.02 (m, 2H), 3.14 (m, 1H), 3.50 (m, 1H), 3.64 (m, 1H), 3.73 (m, 1H), 3.81

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(m, 3H), 4.87 (m, 1H), 5.00 (m, 1H), 6.98 (m, 1H), 7.08 (m, 1H), 7.15 (m, 1H), 7.26 (m, 6H). MS (ESI): 534 (MH<sup>+</sup>).

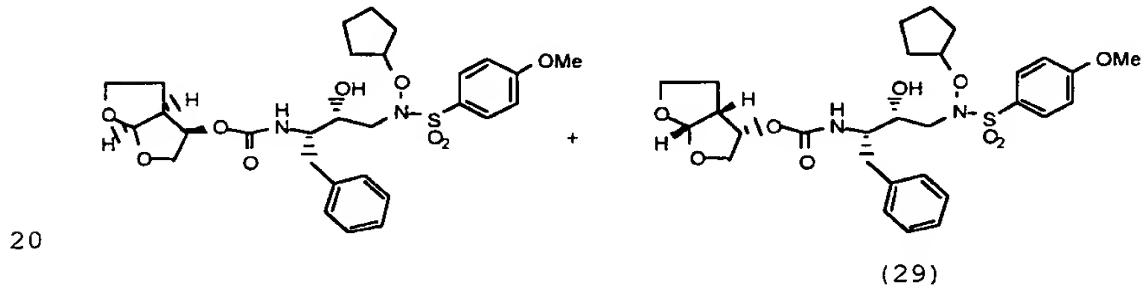
Example 28



(3S,3aR,7aS)hexahydro-4H-furo[2,3-b]pyran-3-yl N-((1S,2R)-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate and 3R,3aS,7aR)hexahydro-4H-furo[2,3-b]pyran-3-yl N-((1S,2R)-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate. A mixture of (3R,3aS,7aR)+(3S,3aR,7aS)hexahydro-4H-furo[2,3-b]pyran-3-yl (4-nitrophenyl) carbonate (68 mg, 0.219 mmol), N<sup>3</sup>-[(2R,3S)-3-amino-2-hydroxy-4-phenylbutyl]-N<sup>1</sup>-(cyclopentyloxy)-4-methoxy-1-benzenesulfonamide x trifluoracetic acid (Step 1, Example 48), (60 mg, 0.109 mmol) and N,N-diisopropylethylamine (66.8  $\mu$ L, 0.385 mmol) were combined in approximately 1.5 mL of acetonitrile and stirred at ambient temperature under an Argon atmosphere for 18 hours. An additional quantity of carbonate (20 mg, 0.065 mmol) and N,N-diisopropylethylamine (40  $\mu$ L, 0.224 mmol) was added and the reaction mixture was heated at 60°C for 1.5 hours. The reaction was cooled and evaporated *in vacuo*. The residue was dissolved in ethyl acetate and washed three times with 5% w/v potassium carbonate, saturated aqueous brine, dried over anhydrous magnesium sulfate, filtered and evaporated in

vacuo to a residue. The crude product was purified on a preparative TLC plate (20x20 cm, 500  $\mu$ M) eluting with 95:5/methylene chloride:methanol. The product band was removed, eluted with 4:1 methylene chloride : methanol, 5 filtered, and evaporated *in vacuo*. The residue was dissolved in diethylether, evaporated *in vacuo* and dried under high vacuum to provide a 1:1 mixture of (3*S*,3a*R*,7a*S*)hexahydro-4*H*-furo[2,3-*b*]pyran-3-yl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-10 hydroxypropyl)carbamate and 3*R*,3a*S*,7a*R*)hexahydro-4*H*-furo[2,3-*b*]pyran-3-yl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-*hydroxypropyl)carbamate as a foam (55 mg, 83%).  $^1$ H-NMR (chloroform-D3): 1.80 (m, 12H), 2.19 (m, 1H), 3.00 (m, 5H), 3.48 (m, 1H), 3.89 (m, 7H), 4.21 (m, 1H), 4.92 (m, 2H), 5.08 (m, 1H), 5.27 (bm, 1H), 7.04 (m, 2H), 7.28 (m, 5H), 7.76 (m, 2H). MS (ESI): 627 (M+Na). 15*

Example 29

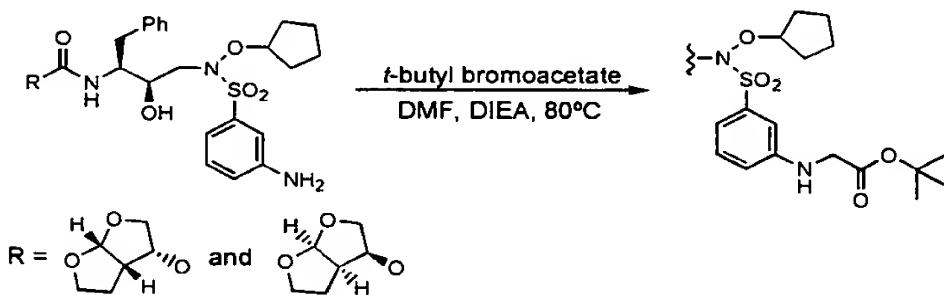


(3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-25 hydroxypropyl)carbamate and (3*S*,3a*R*,6a*S*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate. A mixture of (3*R*,3a*S*,6a*R*) + (3*S*,3a*R*,6a*S*)hexahydrofuro[2,3-

- 120 -

b) furan-3-yl (4-nitrophenyl) carbonate (96.5 mg, 0.327 mmol, WO 9721683), *N*<sup>3</sup>-[(2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl]-*N*<sup>1</sup>-(cyclopentyloxy)-4-methoxy-1-benzenesulfonamide x trifluoracetic acid (Step 1, Example 48), (60 mg, 0.109 mmol) and *N,N*-diisopropylethylamine (85.6  $\mu$ L, 0.491 mmol) were combined in approximately 1.5 mL of acetonitrile and stirred at ambient temperature under an Argon atmosphere for 18 hours. The reaction mixture was evaporated *in vacuo* and the residue was purified on a preparative TLC plate (20x20 cm, 500  $\mu$ M) eluting with 1:1/ethyl acetate:hexane. The product band was removed, eluted with 3:1/methylene chloride:methanol, filtered, and evaporated *in vacuo*. The residue was dissolved in diethylether, evaporated *in vacuo* and dried under high vacuum to provide a 1:1 mixture of (3*R*,3*aS*,6*aR*)hexahydrofuro [2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate and (3*S*,3*aR*,6*aS*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate (50 mg, 26%) as a foam.  $^1$ H-NMR (chloroform-D3): 1.68 (m, 10H), 2.95 (m, 6H), 3.64 (m, 2H), 3.88 (s, 3H), 3.93 (m, 4H), 4.82 (m, 2H), 5.01 (bm, 1H), 5.65 (m, 1H), 6.98 (m, 2H), 7.23 (m, 5H), 7.71 (m, 2H). MS (ESI): 613 (M+Na).

25

Example 30

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tert-butyl 2-(3-[(2R,3S)-3-((3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yloxy]carbonylamino)-2-hydroxy-4-

phenylbutyl](cyclopentyloxy)amino]sulfonylanilino)acetate

and tert-butyl 2-(3-[(2R,3S)-3-((3S,3aR,6aS)hexahydrofuro

5 [2,3-b]furan-3-yloxy]carbonylamino)-2-hydroxy-4-phenylbutyl](cyclopentyloxy)amino]sulfonylanilino)acetate

A solution of 0.250 g (0.434 mmol) of a 1:1 mixture of

(3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl N-((1S,2R)-1-

benzyl-3-(cyclopentyloxy)[(3-aminophenyl)sulfonyl]amino-2-

10 hydroxypropyl)carbamate and (3S,3aR,6aS)hexahydrofuro[2,3-b]furan-3-yl N-((1S,2R)-1-benzyl-3-(cyclopentyloxy)[(3-

aminophenyl)sulfonyl]amino-2-hydroxypropyl)carbamate (see example 31), 0.13 mL (0.87 mmol) of tert-butyl bromoacetate, and 0.15 mL (0.87 mmol) of *N,N*-diisopropylethylamine in 5 mL

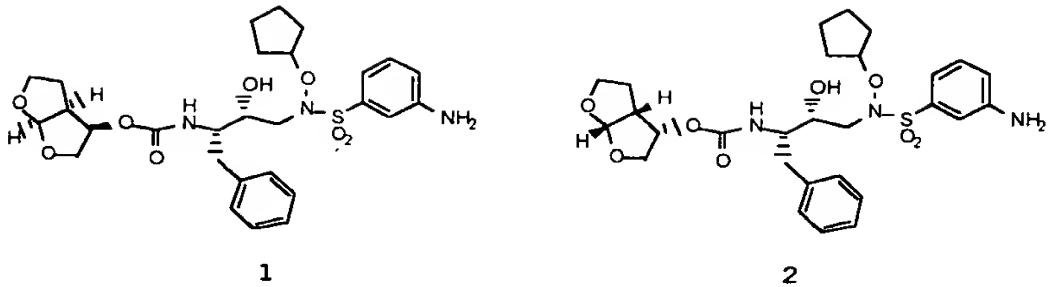
15 of anyhydrous DMF was stirred at 80°C for 18 hours. The solution was cooled to RT and concentrated *in vacuo*. The residue was dissolved in dichloromethane. The solution was washed with saturated aqueous brine (3x), dried over anhydrous MgSO<sub>4</sub>, and concentrated *in vacuo*. The crude

20 product was purified by flash chromatography (silica gel, 4:6 hexane/EtOAc) to afford 0.28 g (94%) of the desired product as a light yellow foam. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 7.31-7.07 (7H), 6.93-6.80 (3H), 6.61 (1H), 5.47 (1H), 5.19 (1H), 4.83-4.64 (2H), 3.81-3.40 (7H), 3.06-2.60 (5H), 2.53-2.27 (1H),

25 1.95-1.16 (19H). LCMS(ESI): 690 (M+H).

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**Example 31**



5

(31)

(3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(3-aminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate (1) and

(3S,3aR,6aS) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(3-aminophenyl)sulfonyl] (cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate (2) as a white lyophile. A mixture of (3*R*,3a*S*,6a*R*) + (3*S*,3a*R*,6a*S*) hexahydrofuro[2,3-*b*]furan-3-yl (4-nitrophenyl) carbonate (211 mg, 0.716 mmol), 3-amino-*N*<sup>1</sup>-[(2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl]-*N*<sup>2</sup>-(cyclopentyloxy)-1-benzenesulfonamide (Step 1, Example 27), (100 mg, 0.239 mmol), and *N,N*-diisopropylethylamine (166.4  $\mu$ L, 0.955 mmol) were combined in approximately 3 mL of acetonitrile and stirred at ambient temperature under an Argon atmosphere for approximately 18 hours. The reaction mixture was evaporated *in vacuo* and purified on two preparative silica TLC plates (20x20 cm, 1000  $\mu$ M) eluting with 93:7/methylene chloride:methanol. The product band was removed, eluted with 4:1/methylene chloride:methanol, filtered, and evaporated *in vacuo*. The residue was partitioned between 1N NaOH and dichloromethane. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried

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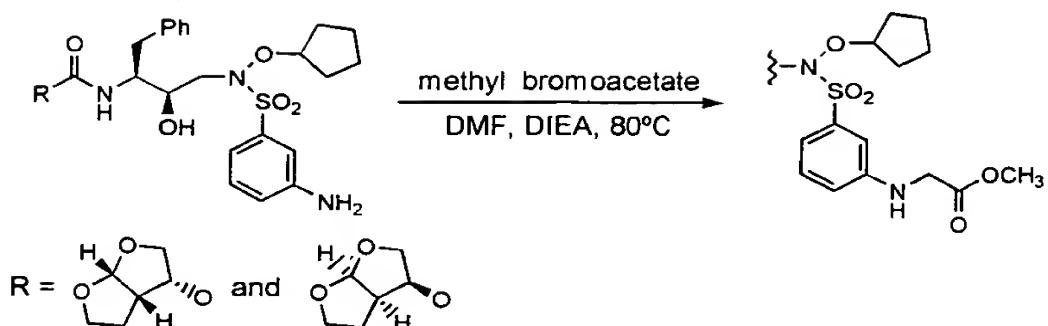
over anhydrous magnesium sulfate, filtered and evaporated *in vacuo* to a foam. The mixture of diastereomers were separated by supercritical fluid chromatography [Chiralpak AD (2 cm, Chiral Technologies), 21 Mpa; 11.3 mL/min 5 methanol+0.1% triethylamine; 45 g/min CO<sub>2</sub>; 40°C.]. The fraction containing the diastereomer possessing a shorter retention time was evaporated *in vacuo* to a residue and then purified again by preparative TLC as above. The product was lyophilized from acetonitrile and water to provide 10 (3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(3-aminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate (1) as a white lyophile (18 mg, 13%). The fraction containing the diastereomer possessing a longer retention time was evaporated *in vacuo* to a residue and then 15 purified again by preparative TLC as above. The product was lyophilized from acetonitrile and water to provide (3*S*,3a*R*,6a*S*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(3-aminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate (2) as a white lyophile (18 mg, 13%). 20 1 H-NMR (methanol-D4) 1.62 (m, 10H), 2.52 (m, 1H), 2.88 (m, 2H), 3.10 (m, 2H), 3.62 (m, 2H), 3.76 (m, 3H), 3.87 (m, 1H), 4.81 (m, 1H), 4.90 (m, 1H), 5.55 (d, 1H), 6.93 (m, 1H), 7.02 (m, 1H), 7.08 (m, 1H), 7.14 (m, 1H), 7.21 (m, 5H). MS(ESI): 598(M+Na). 25 2 H-NMR (methanol-D4): 1.73 (m, 10H), 2.57 (m, 1H), 2.93 (m, 2H), 3.09 (m, 2H), 3.46 (m, 1H), 3.79 (m, 5H), 4.84 (m, 2H), 5.57 (d, 1H), 6.92 (m, 1H), 7.02 (m, 1H), 7.09 (m, 1H), 7.20 (m, 6H). MS(ESI): 598(M+Na).

30

Example 32

Step 1:

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5 **methyl 2-[(2R,3S)-3-[(3R,3aS,6aR)hexahydrofuro[2,3-**

**b]furan-3-yloxy]carbonylamino)-2-hydroxy-4-**

**phenylbutyl](cyclopentyloxy)amino]sulfonylanilino)acetate**

10 **and methyl 2-[(2R,3S)-3-[(3S,3aR,6aS)hexahydrofuro[2,3-**

**b]furan-3-yloxy]carbonylamino)-2-hydroxy-4-**

**phenylbutyl](cyclopentyloxy)amino]sulfonylanilino)acetate.**

A solution of 0.500 g (0.869 mmol) of a 1:1 mixture of

15 (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl N-((1S,2R)-1-

benzyl-3-(cyclopentyloxy)[(3-aminophenyl)sulfonyl]amino-2-

hydroxypropyl carbamate and (3S,3aR,6aS)hexahydrofuro[2,3-

b]furan-3-yl N-((1S,2R)-1-benzyl-3-(cyclopentyloxy)[(3-

aminophenyl)sulfonyl]amino-2-hydroxypropyl carbamate (see

20 example 31), 0.250 mL (2.61 mmol) of methyl bromoacetate, and 0.450 mL (2.61 mmol) of *N,N*-diisopropylethylamine in 5

mL of anhydrous DMF was stirred at 80° C for 18 hours. The solution was cooled to RT and concentrated *in vacuo*. The residue was dissolved in ethyl acetate. The solution was

25 washed with saturated aqueous brine (3x), dried over anhydrous MgSO<sub>4</sub>, and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel,

97:3 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to afford 0.50 g (89%) of the desired

product as a light yellow foam. H<sub>1</sub>-NMR (DMSO-d<sub>6</sub>): 7.38-7.08

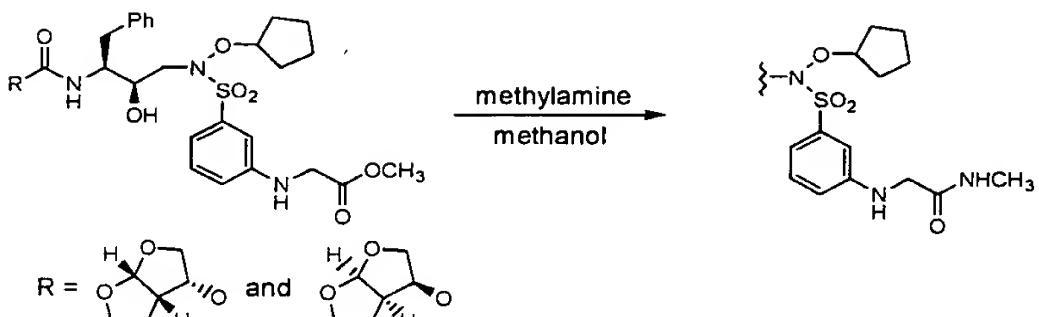
25 (7H), 7.01-6.85 (3H), 6.71 (1H), 5.52 (1H), 5.21 (1H), 4.88-

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4.70 (2H), 3.99 (2H), 3.88-3.46 (8H), 3.13-2.64 (5H), 2.57-2.35 (1H), 2.01-1.17 (10H). LCMS (ESI): 648 (M+H).

Step 2:

5



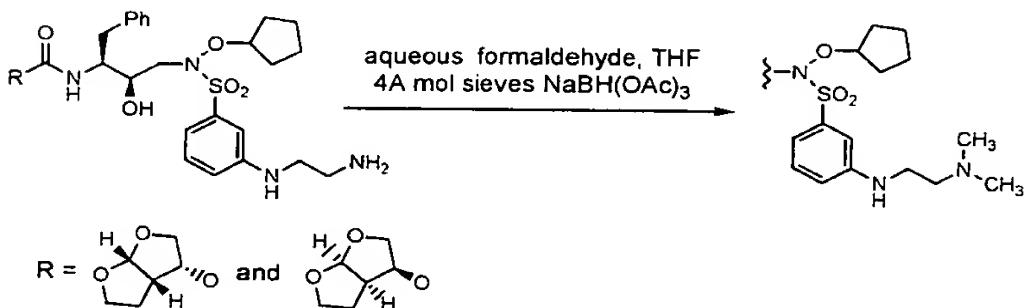
(3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(3-[2-(methylamino)-2-oxoethyl]aminophenyl)sulfonyl]amino-2-hydroxypropyl)carbamate and (3*S*,3a*R*,6a*S*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(3-[2-(methylamino)-2-oxoethyl]aminophenyl)sulfonyl]amino-2-hydroxypropyl)carbamate. A solution of 50.0 mg (0.0770 mmol) of a 1:1 mixture of methyl 2-(3-[(2*R*,3*S*)-3-((3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yloxy]carbonylamino)-2-hydroxy-4-phenylbutyl] (cyclopentyloxy) amino)sulfonylanilino)acetate and methyl 2-(3-[(2*R*,3*S*)-3-((3*S*,3a*R*,6a*S*)hexahydrofuro[2,3-*b*]furan-3-yloxy]carbonyl amino)-2-hydroxy-4-phenylbutyl] (cyclopentyloxy) amino) sulfonylanilino)acetate in 5 mL of 2M methylamine in MeOH was stirred at RT in a sealed tube. After 4 hours the solution was concentrated *in vacuo* and the residue subjected to flash chromatography (silica gel, 97:3 EtOAc/MeOH) to afford 38 mg (76%) of the

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desired product as a white foam.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 7.53-7.00 (11H), 6.80-6.59 (1H), 6.68 (1H), 5.50-5.18 (1H), 5.06 (1H), 4.85 (1H), 4.09-3.60 (7H), 3.28-2.78 (8H), 2.00-1.47 (10H).  $\text{MS}(\text{ESI})$ : 647 ( $\text{M}+\text{H}$ ), 669 ( $\text{M}+\text{Na}$ ).

5

Example 33



10

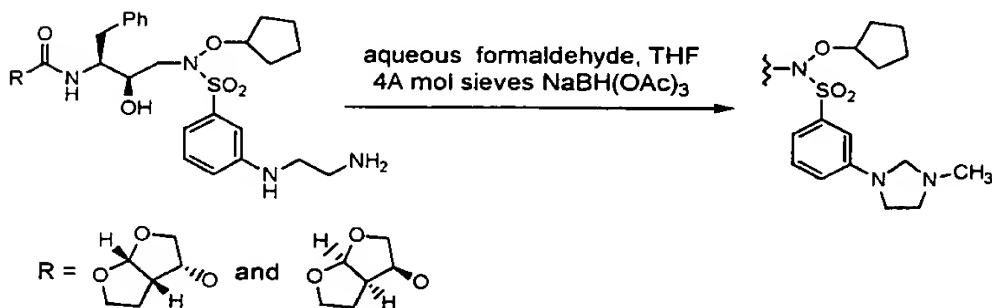
(3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(3-[2-(dimethylamino)ethyl]aminophenyl)sulfonyl]amino-2-hydroxypropyl)carbamate and (3*S*,3a*R*,6a*S*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(3-[2-(dimethylamino)ethyl]aminophenyl)sulfonyl]amino-2-hydroxypropyl)carbamate.

A solution of 65.0 mg (0.110 mmol) of a 1:1 mixture of (3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(3-[(2-aminoethyl)amino]phenylsulfonyl)(cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate and (3*S*,3a*R*,6a*S*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(3-[(2-aminoethyl)amino]phenylsulfonyl)(cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate (see example 83), 0.050 mL (0.55 mmol) of 37% aqueous formaldehyde, and 0.117 g (0.550 mmol) of  $\text{NaBH}(\text{OAc})_3$  was treated with 0.150 g of powdered 4A molecular sieves and the mixture was stirred at RT. After

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stirring at RT for 18 hours, tlc (silica gel, 9:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) indicated complete loss of starting material at R<sub>f</sub>=0.05 and two new components at R<sub>f</sub>=0.31 and 0.63. The reaction mixture was filtered and the filtrate concentrated to dryness. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub>. The solution was washed with saturated aqueous NaHCO<sub>3</sub> (3x), dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The crude product was subjected to flash chromatography (silica gel, 95:5 to 90:10 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to afford 14 mg (20%) of the R<sub>f</sub>=0.31 product as a white foam. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.37-7.11 (8H), 7.10-6.90 (2H), 6.85 (1H), 5.62 (1H), 5.18-4.89 (2H), 4.79 (1H), 4.00-3.49 (5H), 3.32-2.60 (10H), 2.38 (6H), 1.94-1.40 (10H). LCMS (ESI): 647 (M+H).

15

Example 34

(34)

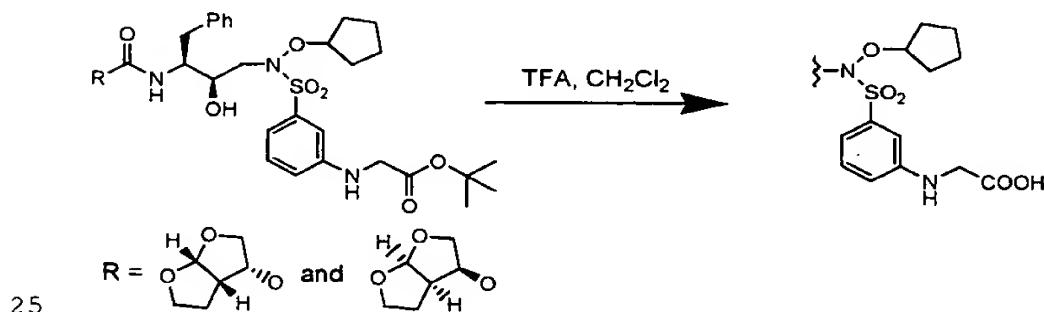
(3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-benzyl-3-((cyclopentyloxy)[3-(3-methyl-1-imidazolidinyl)phenyl]sulfonylamino)-2-hydroxypropyl]carbamate and (3*S*,3*aR*,6*aS*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-benzyl-3-((cyclopentyloxy)[3-(3-methyl-1-imidazolidinyl)phenyl]sulfonylamino)-2-hydroxypropyl]carbamate

A solution of 65.0 mg (0.110 mmol) of a 1:1 mixture of (3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(3-

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[(2-aminoethyl)amino]phenylsulfonyl) (cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate and (3*S*, 3*a**R*, 6*a**S*)hexahydrofuro[2,3-*b*]furan-3-yl N-(1*S*, 2*R*)-3-[(3-[(2-aminoethyl)amino]phenylsulfonyl) (cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate (see example 83), 0.050 mL (0.55 mmol) of 37% aqueous formaldehyde, and 0.117 g (0.550 mmol) of NaBH(OAc)<sub>3</sub> was treated with 0.150 g of powdered 4A molecular sieves and the mixture stirred at RT. After stirring at RT for 18 hours, tlc (silica gel, 9:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) indicated complete loss of starting material at R<sub>f</sub>=0.05 and two new components at R<sub>f</sub>=0.31 and 0.63. The reaction mixture was filtered and the filtrate concentrated to dryness. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub>. The solution was washed with saturated aqueous NaHCO<sub>3</sub> (3x), dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The crude product was subjected to flash chromatography (silica gel, 95:5 to 90:10 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to afford 20 mg (28%) of the R<sub>f</sub>=0.63 product as a white foam. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.40-7.01 (8H), 6.88 (1H), 6.70 (1H), 5.62 (1H), 5.06-4.73 (3H), 4.21-3.39 (7H), 3.23-2.62 (10H), 2.52 (3H), 1.93-1.20 (10H). LCMS (ESI): 645 (M+H).

Example 35



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2-2-((2R,3S)-3-((3R,3aS,6aR)hexahydrofuro[2,3-*b*]furan-3-yloxy)carbonylamino)-hydroxy-4-phenylbutyl](cyclopentyloxy)amino]sulfonylanilino)acetic acid and 2-2-((3-((2R,3S)-3-((3S,3aR,6aS)hexahydrofuro[2,3-*b*]furan-3-yloxy)carbonylamino)-hydroxy-4-phenylbutyl](cyclopentyloxy)amino]sulfonylanilino)acetic acid.

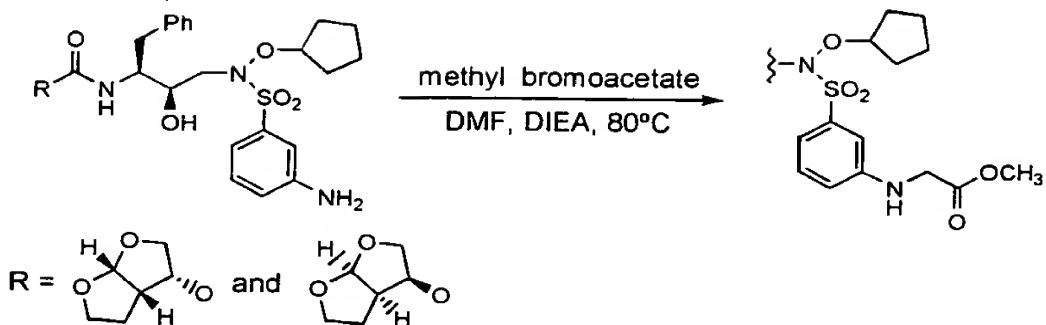
5 A solution of 0.218 g (0.316 mmol) of a 1:1 mixture of *tert*-butyl 2-((2R,3S)-3-((3R,3aS,6aR)hexahydrofuro[2,3-*b*]furan-3-yloxy)carbonylamino)-2-hydroxy-4-phenylbutyl](cyclopentyloxy)amino]sulfonylanilino)acetate and *tert*-butyl 2-((3-((2R,3S)-3-((3S,3aR,6aS)hexahydrofuro[2,3-*b*]furan-3-yloxy)carbonylamino)-2-hydroxy-4-phenylbutyl](cyclopentyloxy)amino]sulfonylanilino)acetate (see example 30) in 5 mL of CH<sub>2</sub>Cl<sub>2</sub> was treated with 6 mL of trifluoroacetic acid. After stirring at RT for 2 hours tlc (silica gel, hexane/EtOAc) indicated complete loss of starting material and the formation of a new more polar 10 product. The solution was concentrated *in vacuo*. The residue was dissolved in a minimum volume of CH<sub>2</sub>Cl<sub>2</sub> and the solution added dropwise to rapidly stirred 4:1 hexane/ether. An off-white solid precipitated which was collected by 15 filtration and dried *in vacuo*. yield=0.183 g (92%). H<sub>1</sub>-NMR (DMSO-d<sub>6</sub>): 7.25-7.05 (7H), 6.87 (3H), 6.53 (1H), 5.46 (1H), 5.16 (1H), 4.82-4.65 (2H), 3.83-3.23 (7H), 3.08-2.60 (5H), 2.38 (1H), 1.91-1.04 (10H). MS(ESI): 634 (M+H), 656 (M+Na).

Example 36

30

Step 1:

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methyl 2-[(2R,3S)-3-[(3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yloxy]carbonylamino]-2-hydroxy-4-

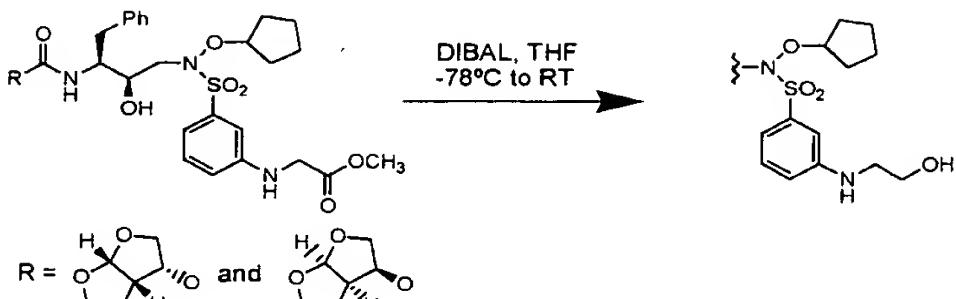
5 phenylbutyl](cyclopentyloxy)amino]sulfonylanilino)acetate  
 and methyl 2-[(2R,3S)-3-[(3S,3aR,6aS)hexahydrofuro[2,3-b]furan-3-yloxy]carbonylamino]-2-hydroxy-4-  
 phenylbutyl](cyclopentyloxy)amino]sulfonylanilino)acetate  
 A solution of 0.500 g (0.869 mmol) of a 1:1 mixture of  
 10 (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl N-((1S,2R)-1-  
 benzyl-3-(cyclopentyloxy)[(3-aminophenyl)sulfonyl]amino-2-  
 hydroxypropyl)carbamate and (3S,3aR,6aS)hexahydrofuro[2,3-b]furan-3-yl N-((1S,2R)-1-benzyl-3-(cyclopentyloxy)[(3-  
 aminophenyl)sulfonyl]amino-2-hydroxypropyl)carbamate (see  
 15 example 31), 0.250 mL (2.61 mmol) of methyl bromoacetate,  
 and 0.450 mL (2.61 mmol) of *N,N*-diisopropylethylamine in 5  
 mL of anyhydrous DMF was stirred at 80°C for 18 hours. The  
 solution was cooled to RT and concentrated *in vacuo*. The  
 residue was dissolved in ethyl acetate. The solution was  
 20 washed with saturated aqueous brine (3x), dried over  
 anhydrous MgSO<sub>4</sub>, and concentrated *in vacuo*. The crude  
 product was purified by flash chromatography (silica gel,  
 97:3 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to afford 0.50 g (89%) of the desired  
 product as a light yellow foam. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 7.38-7.08  
 25 (7H), 7.01-6.85 (3H), 6.71 (1H), 5.52 (1H), 5.21 (1H), 4.88-

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4.70 (2H), 3.99 (2H), 3.88-3.46 (8H), 3.13-2.64 (5H), 2.57-2.35 (1H), 2.01-1.17 (10H). LCMS (ESI): 648 (M+H).

Step 2:

5

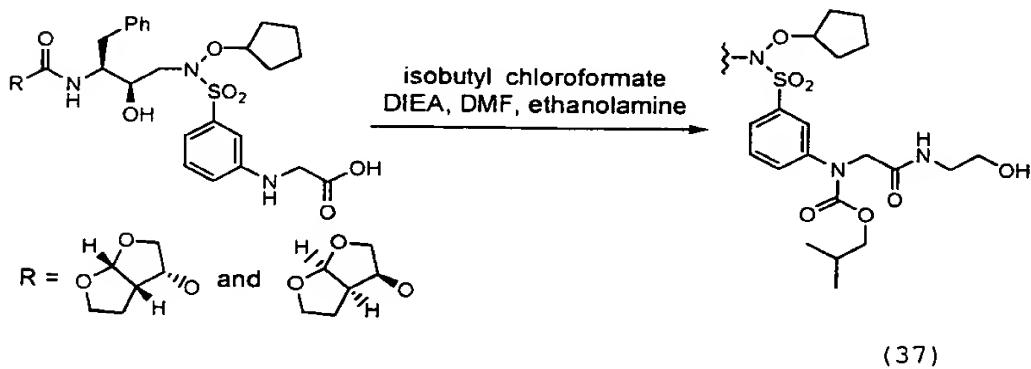


(3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-

10 *benzyl*-3-[(cyclopentyloxy)(3-[(2-  
hydroxyethyl)amino]phenylsulfonyl)amino]-2-  
hydroxypropylcarbamate and (3*S*,3a*R*,6a*S*)hexahydrofuro[2,3-  
b]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-[(cyclopentyloxy)(3-[(2-  
hydroxyethyl)amino]phenylsulfonyl)amino]-2-  
15 hydroxypropylcarbamate. A solution of 0.100 g (0.154 mmol)  
of a 1:1 mixture of methyl 2-(3-[(2*R*,3*S*)-3-  
([(3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-  
yloxy]carbonylamino)-2-hydroxy-4-  
phenylbutyl](cyclopentyloxy)amino)sulfonylanilino)acetate  
20 and methyl 2-(3-[(2*R*,3*S*)-3-([(3*S*,3a*R*,6a*S*)hexahydrofuro[2,3-  
b]furan-3-yloxy]carbonyl amino)-2-hydroxy-4-  
phenylbutyl](cyclopentyloxy)amino)sulfonylanilino)acetate  
in 10 mL of anhydrous THF at -78°C was treated with 0.23 mL  
(0.34 mmol) of 1.5 M diisobutylaluminum hydride in toluene  
25 by dropwise addition. The solution was allowed to warm to  
RT. The reaction progress was monitored by tlc (silica gel,  
hexane/EtOAc). Two additional 0.30 mL aliquots of DIBAL

solution were added at 1 hour intervals (cooling the reaction vessel to -78°C each time) to induce complete loss of starting material. After 2 additional hours the reaction mixture was mixed with 25 mL of saturated potassium sodium tartrate and stirred vigorously for 30 minutes. The mixture was diluted with water and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x). The combined extracts were washed with water (3x), dried over anhydrous MgSO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 99:1 EtOAc/MeOH) to afford 25 mg (26%) of the desired product as a white foam. H<sub>1</sub>-NMR (CDCl<sub>3</sub>): 7.40-7.03 (10H), 6.92 (1H), 5.62 (1H), 5.13-4.88 (2H), 4.81 (1H), 3.96-3.44 (8H), 3.32 (2H), 3.22-2.59 (6H), 1.90-1.20 (10H). LCMS (ESI): 620 (M+H).

15

Example 37

20 (3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-[(cyclopentyloxy)(3-[2-[(2-hydroxyethyl)amino]-2-oxoethyl(isobutoxycarbonyl)amino]phenylsulfonyl)amino]-2-hydroxypropylcarbamate and (3*S*,3a*R*,6a*S*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-[(cyclopentyloxy)(3-[2-  
25 [(2-hydroxyethyl)amino]-2-

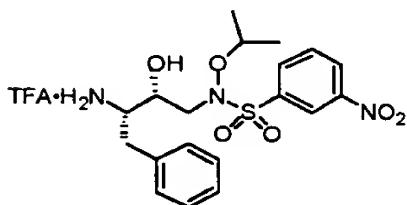
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**oxoethyl(isobutoxycarbonyl)amino]phenylsulfonyl)amino]-2-hydroxypropylcarbamate.**

A solution of 60.0 mg (0.0947 mmol) of a 1:1 mixture of 2-2-(3-[(2R,3S)-3-((3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yloxy]carbonylamino)-hydroxy-4-phenylbutyl](cyclopentyloxy)amino]sulfonylanilino)acetic acid and 2-2-(3-[(2R,3S)-3-((3S,3aR,6aS)hexahydrofuro[2,3-b]furan-3-yloxy]carbonylamino)-hydroxy-4-phenylbutyl](cyclopentyloxy)amino]sulfonylanilino)acetic acid (see example 35) in 3 mL of anhydrous DMF at 0°C was treated with 0.033 mL (0.19 mmol) of *N,N*-diisopropylethylamine followed by 0.025 mL (0.19 mmol) of isobutyl chloroformate. After stirring at 0°C for 15 minutes the reaction was treated with 3 drops (excess) of ethanalamine. After warming to RT and stirring for 18 hours the solution was concentrated to dryness. The residue was purified by flash chromatography (silica gel, 93:7 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to afford 66 mg (90%) of the desired compound as a white foam. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 8.05 (1H), 7.80 (1H), 7.69 (1H), 7.63-7.50 (2H), 7.24-7.02 (5H), 6.96 (1H), 5.47 (1H), 5.21 (1H), 4.80-4.67 (2H), 4.63 (1H), 4.56 (1H), 4.20 (2H), 3.82-3.20 (8H), 3.10 (2H), 3.05-2.35 (8H), 1.88-1.10 (11H), 0.90-0.72 (6H). LCMS (ESI): 777 (M+H).

Example 38

25 Step 1:

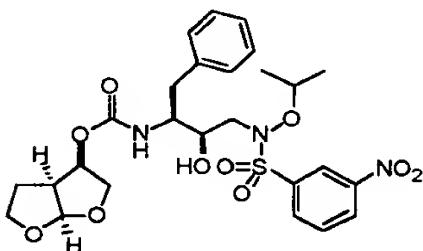


**(1*S*,2*R*)-1-benzyl-3-(isopropoxy)[(3-nitrophenyl)sulfonyl]amino-2-hydroxypropylamine**

**•trifluoroacetic salt.** *tert*-Butyl-N-((1*S*,2*R*)-1-benzyl-3-(isopropoxy)[(3-nitrophenyl)sulfonyl]amino-2-

5 hydroxypropyl)carbamate (1.37 g, 2.62 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL). Trifluoroacetic acid (10 mL) was added at 0°C with stirring and the reaction was stirred 2h at room temperature. The solvent was removed by evaporation and was kept under vacuum. The product was used without 10 purification.

Step 2:

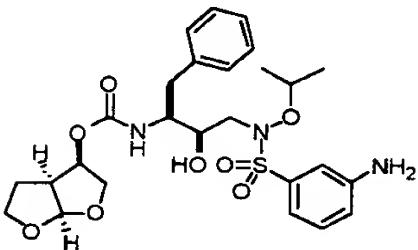


15 **(3*R*,3a*S*,6a*R*) Hexahydrofuro[2,3b]furan-3-yl-N-((1*S*,2*R*)-1-benzyl-3-(isopropoxy)[(3-nitrophenyl)sulfonyl]amino-2-hydroxypropyl)carbamate.** (1*S*,2*R*)-1-benzyl-3-(isopropoxy)[(3-nitrophenyl)sulfonyl]amino-2-hydroxypropylamine•trifluoroacetic acid (305 mg, 0.57 mmol) 20 was combined with (3*R*,3a*S*,6a*R*) Hexahydrofuro[2,3b]furan-3-yl (4-nitrophenyl) carbonate (184 mg, 0.62 mmol) in anhydrous CH<sub>3</sub>CN (8 mL) under a N<sub>2</sub> atmosphere. Triethylamine (400  $\mu$ L, 2.8 mmol) was added and the reaction was stirred at 50°C for 16 hours. Reaction mixture was diluted in EtOAc and washed 25 with water and brine. The organic phase was dried with MgSO<sub>4</sub> and solvent was removed in vacuo. Purification by flash chromatography (30% EtOAc / Hex). Recovered 204 mg (62%) of the product as a white foam. HPLC showed the

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material to be 98% pure; Ret. time = 10.10 min.  $^1\text{H}$  NMR (CDCl<sub>3</sub>): 8.60 (s, 1H), 8.46 (m, 1H), 8.02 (m, 1H), 7.72 (m, 1H), 7.10-7.23 (m, 5H), 5.58 (m, 1H), 4.97 (m, 1H), 4.80 (m, 1H), 4.94 (m, 1H), 4.50-4.55 (m, 1H), 3.77-3.96 (m, 4H), 5 3.59-3.64 (m, 2H), 2.70-2.97 (m, 5H), 1.60 (m, 1H), 1.45 (m, 1H), 1.21 (m, 6H). MS (ES+): Obs M+H @ 580.1 amu.

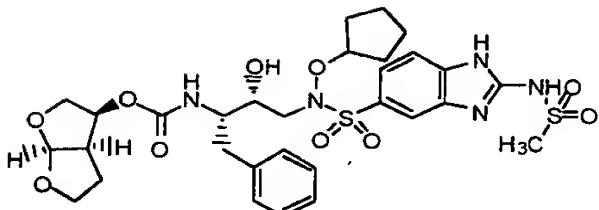
Step 3:



10

(3R,3aS,6aR) Hexahydrofuro[2,3b]furan-3-yl-N-(1S,2R)-1-benzyl-3-[(isopropoxy) [(3-aminophenyl)sulfonyl]amino-2-hydroxypropylcarbamate.

15 (3R,3aS,6aR) Hexahydrofuro[2,3b]furan-3-yl-N-(1S,2R)-1-benzyl-3-[(isopropoxy) [(3-nitrophenyl)sulfonyl]amino-2-hydroxypropylcarbamate (100 mg, 0.17 mmol) was added in 10 mL of NH<sub>3</sub> (2N) in MeOH. To this solution was added 100 mg of 10 % Pd/C. The hydrogenation was performed under 30 psi 20 of hydrogen over 30 minutes. The catalyst was removed by filtration through a pad of celite. The solvent was removed *in vacuo*. Recovered 91 mg (96%) of the product as a white foam. HPLC showed the material to be 98% pure; Ret. time = 9.12 min.  $^1\text{H}$  NMR (CDCl<sub>3</sub>): 7.09-7.24 (m, 9H), 7.00 (s, 1H), 25 6.84 (m, 1H), 5.58 (d, 1H), 4.97 (m, 1H), 4.78 (m, 1H), 4.44-4.48 (m, 1H), 3.77-3.91 (m, 5H), 3.64 (m, 2H), 2.71-3.10 (m, 6H), 1.44-1.62 (2x m, 2H), 1.17 (d, 6H). MS (ES+): Obs M+H @ 550.2 amu.

Example 39

(39)

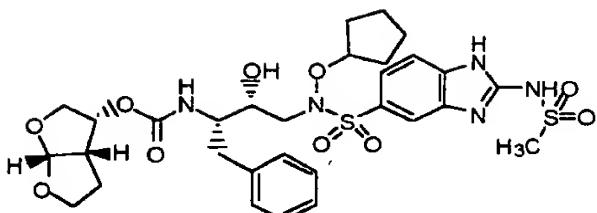
5

**(3*S*,3a*R*,6a*S*) Hexahydrofuro[2,3-b]furan-3-yl-N-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)(2-**

**[(methylsulfonyl)amino]benzimidazol-5-ylsulfonyl)amino-2-hydroxypropyl)carbamate.** (3*S*,3a*R*,6a*S*) Hexahydrofuro[2,3-

10 b) furan-3-yl-N-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)amino-2-hydroxypropyl)carbamate (0.050 g, 0.1 mmol) was combined with 2-[(methylsulfonyl)amino]benzimidazol-5-ylsulfonyl chloride (0.055 g, 0.2 mmol) in anhydrous DMF (1 ml) under a N<sub>2</sub> atmosphere. The resulting solution was chilled to 0°C  
 15 and diisopropylethylethyl amine (0.062 ml, 0.4 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 24 hours. Reaction mixture was diluted in EtOAc and washed with sat. NaHCO<sub>3</sub>, 0.5N KHSO<sub>4</sub> and brine. Organic phase was dried with MgSO<sub>4</sub> and solvent was removed  
 20 *in vacuo*. Purification by preparative TLC (5% MeOH/EtOAc). Recovered 0.051 g (62%) of the product as a white foam. R<sub>f</sub>= 0.42 (5% MeOH/EtOAc). <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.09 (1H, s), 7.76 (1H, d), 7.39 (1H, d), 7.32-7.12 (5H, m), 6.54-6.40 (2H, m), 5.67 (1H, d), 5.10-4.92 (2H, m), 4.85 (1H, m), 4.00-3.83  
 25 (3H, m), 3.82-3.70 (2H, m), 3.62-3.51 (1H, m), 3.38 (1H, m), 3.31 (3H, s), 3.10 (1H, m), 3.04-2.80 (4H, m), 1.92-1.70 (6H, m), 1.69-1.44 (4H, m). LRMS (M+H)<sup>+</sup> 694.1.

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Example 40

(40)

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(3R, 3aS, 6aR) Hexahydrofuro[2,3-b]furan-3-yl-N-((1S, 2R)-1-benzyl-3-(cyclopentyloxy)(2-

[(methylsulfonyl)amino]benzimidazol-5-ylsulfonyl)amino-2-hydroxypropyl carbamate.

(3R, 3aS, 6aR) Hexahydrofuro[2,3-b]furan-3-yl-N-((1S, 2R)-1-benzyl-3-(cyclopentyloxy)amino-2-hydroxypropyl)carbamate (Step 2, Example 54), (0.065 g, 0.2 mmol) was combined with 2-

[(methylsulfonyl)amino]benzimidazol-5-ylsulfonyl chloride (0.071 g, 0.2 mmol) in anhydrous DMF (2 ml) under a N<sub>2</sub>

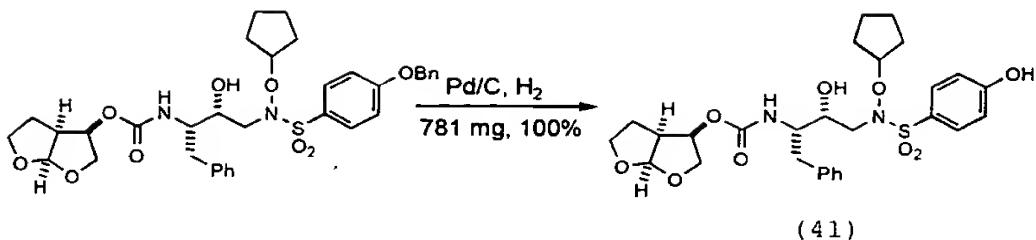
atmosphere. The resulting solution was chilled to 0°C and diisopropylethyl amine (0.080 ml, 0.5 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 24 hours. Reaction mixture was diluted in EtOAc and washed with sat. NaHCO<sub>3</sub>, 0.5N KHSO<sub>4</sub> and brine. Organic

phase was dried with MgSO<sub>4</sub> and solvent was removed in vacuo. Purification by preparative TLC (5% MeOH/EtOAc). Recovered 0.051 g (62%) of the product as a white foam. R<sub>f</sub> = 0.53 (5% MeOH/EtOAc).

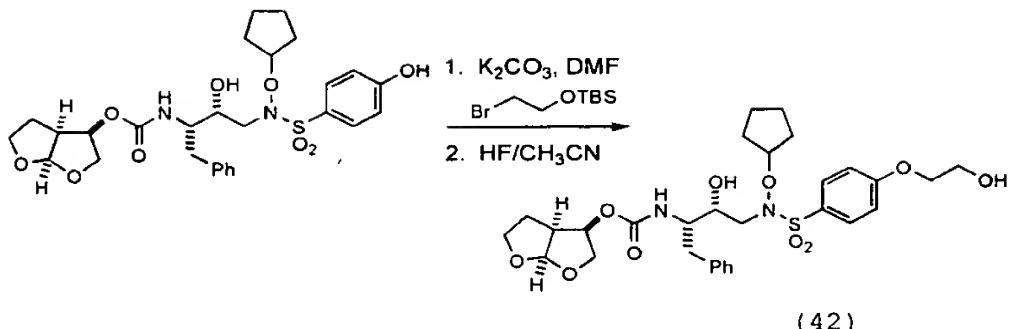
<sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.09 (1H, s), 7.69 (1H, d), 7.43 (1H, d), 7.32-7.08 (5H, m), 6.31-6.18 (2H, m), 5.71-5.59

(2H, m), 5.10-4.92 (2H, m), 4.85 (1H, m), 4.00-3.83 (3H, m), 3.82-3.70 (2H, m), 3.62-3.51 (1H, m), 3.38 (1H, m), 3.31 (3H, s), 3.10 (1H, m), 3.04-2.80 (4H, m), 1.92-1.70 (6H, m), 1.69-1.44 (4H, m). LRMS (M+H)<sup>+</sup> 694.0.

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Example 41

5 (3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(4-hydroxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate. (3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-[(4-(benzyloxy)phenyl)sulfonyl(cyclopentyloxy) amino]-2-hydroxypropylcarbamate (Example 95), (1.4 mmol, 903 mg) was stirred vigorously with 10% palladium on carbon (200 mg), glacial acetic acid (2.8 mmol, 0.156 mL) and ethyl acetate (1 mL) under hydrogen for 20 hours at room temperature. The reaction was filtered and the filtrate concentrated to produce 781 mg (>99%) of a white solid.  $R_f$  = 0.2 (1:1 hexanes/ethyl acetate); H1-NMR ( $CDCl_3$ ):  $\delta$  7.66 (2H,d), 7.30-7.12 (6H,m), 6.93 (2H,d), 5.78 (1H,bs), 5.66 (1H,s), 4.98 (1H,m), 4.81-4.70 (2H,m), 3.98-3.80 (4H,m), 3.80-3.54 (3H,m), 3.15-2.53 (6H,m), 1.85-1.65 (4H,m), 1.65-1.35 (4H,m); M.S. (ESI)  $M+H=577$ .

Example 42

5

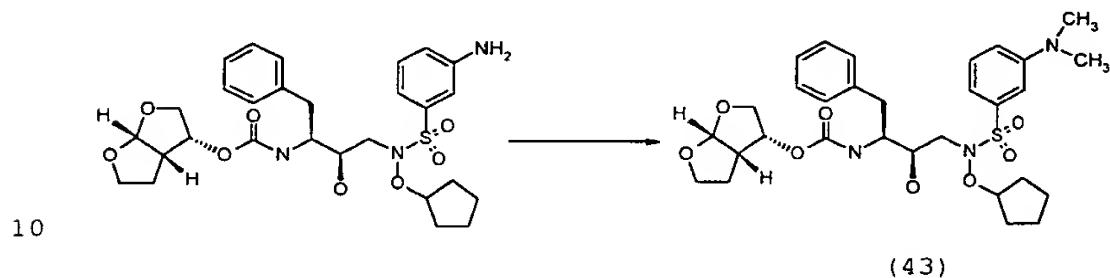
(3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-benzyl-3-((cyclopentyloxy)[4-(2-hydroxyethoxy)phenyl]sulfonylamino)-2-hydroxypropyl]carbamate.

(3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(4-hydroxyphenyl)sulfonyl]amino-2-hydroxypropyl]carbamate (Example 41), (0.13 mmol, 75 mg), (2-bromoethoxy)(tert-butyl)dimethylsilane (0.16 mmol, 37 mg), potassium carbonate (0.40 mmol, 54 mg), and anhydrous DMF (0.5 mL) were stirred at room temperature for 20 hours under nitrogen. The reaction was warmed to 50°C for 2 additional hours. The reaction was concentrated under vacuum, dissolved in ethyl acetate, washed with distilled water and brine, and dried over magnesium sulfate. The crude material was concentrated under vacuum and the resulting clear oil was purified by silica gel flash chromatography (2:1 hexanes/ethyl acetate) to yield 60 mg (63%) of a clear oil. The resulting silyl ether was then stirred in a 3:1 (CH<sub>3</sub>CN/HF(49%)) solution for 1 hour and quenched with a saturated aqueous solution of sodium bicarbonate. The reaction was concentrated under vacuum, dissolved in ethyl acetate, washed with distilled water and brine, and dried over magnesium sulfate. The desired alcohol was crystallized from an ether/hexanes solution

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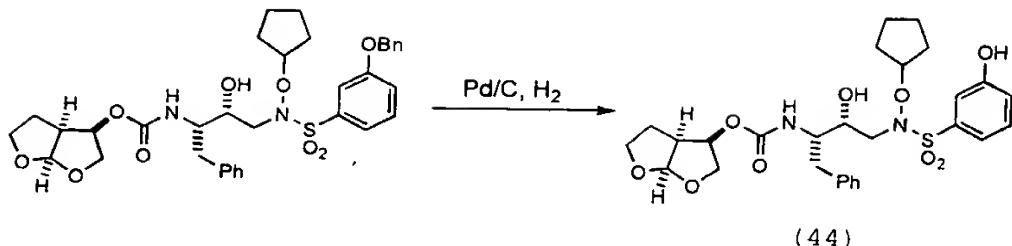
yielding 20 mg (39%) of white powdery crystals.  $R_f = 0.1$  (1:1 hexanes/ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.72 (2H, d), 7.30-7.12 (6H, m), 7.01 (2H, d), 5.64 (1H, s), 4.98 (1H, m), 4.85-4.70 (2H, m), 4.18-4.11 (2H, m), 4.04-3.76 (7H, m), 3.73-5 3.55 (2H, m), 3.10 (1H, bs), 3.04-2.55 (5H, m), 2.10 (1H, m), 1.86-1.68 (4H, m), 1.68-1.44 (4H, m);  $\text{MS}$  (ESI):  $M+\text{H}=621$ .

Example 43



(3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(3-*N,N*-dimethylaminophenyl)sulfonyl](cyclopentyloxy)amino]-1-15 benzyl-2-hydroxypropylcarbamate. A mixture of 58mg (0.1 mMol) of (3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(3-aminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate (Example 77) and 0.25 mL of 37% formaldehyde in 25 mL ethanol was treated with ca.10 20 mg of 5% palladium on carbon and hydrogenated at 50PSI for 20 minutes. The mixture was filtered, evaporated and purified on a 2 inch plug of silica gel (5% methanol-dichloromethane) to give the desired product as a white foam (30mg).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 1.5-1.9 (13H), 2.8 (4H), 2.97 (6H), 3.18 (1H), 3.64 (2H), 3.9 (4H), 4.75-4.95 (4H), 4.99 (1H), 25 5.62 (1H), 6.95 (1H), 7.0-7.4 (8H).  $\text{MS}$ : (LC-MS): 604 ( $\text{MH}^+$ ).

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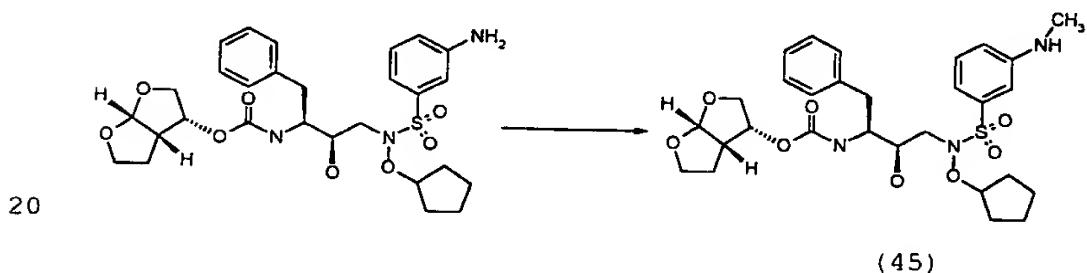
Example 44

5

(3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(3-hydroxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate. This compound was formed (from Example 96) under the same conditions used for

10 (3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(4-hydroxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate (Example 41).  $R_f = 0.2$  (1:1 hexanes/ethyl acetate); H1-NMR (CDCl<sub>3</sub>):  $\delta$  7.43-7.35 (2H, m), 7.30-7.10 (8H, m), 6.63 (1H, bs), 5.70 (1H, s), 5.11-4.95 (2H, m), 4.79 (1H, m), 4.03-3.64 (7H, m), 3.16-2.79 (6H, m), 1.88-1.69 (4H, m), 1.69-1.43 (4H, m); MS (ESI): M+Na=599.

15

Example 45

20 (3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(3-N-methylaminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate. A mixture of 40mg (0.069

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mMol) of (3*R*, 3*aS*, 6*aR*) hexahydrofuro[2, 3-*b*]furan-3-yl *N*-(1*S*, 2*R*)-3-[(3-aminophenyl)sulfonyl](cyclopentyloxy)amino)-1-benzyl-2-hydroxypropylcarbamate (Example 77), 0.0048 mL (0.077 mMol) of iodomethane and 0.014 mL (0.1 5 mMol) of triethylamine in 1 mL of dimethyl formamide was heated to 80°C for 12h. The volatiles were removed in vacuo and the residue was purified by semi-prep C-18 HPLC to give the desired mono-amine as a white solid (8 mg).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 1.5-1.9 (13H), 2.75 (1H), 2.8-3.0 (3H), 2.99 (3H), 10 3.15 (1H), 3.7 (1H), 3.9 (5H), 4.8 (1H), 5.0 (1H), 5.5 (1H), 7.0-7.4 (7H), 7.5 (2H). MS (LC-MS): 590 (M $^+$ ).

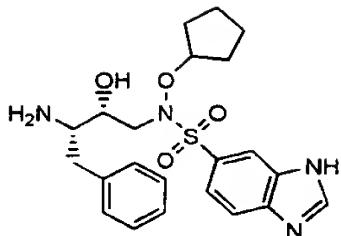
Alternatively this material can also be obtained according to the following method:

15 In a dried flask was introduced 1 eq. of (3*R*, 3*aS*, 6*aR*) Hexahydrofuro[2, 3*b*]furan-3-yl-*N*-(1*S*, 2*R*)-1-benzyl-3-[(cyclopentyloxy)[(3-(*N*-(methyl-*tert*-Butoxycarbonyl))phenyl) 20 sulfonyl]amino-2-hydroxy propylcarbamate (21.5 mg, 0.031 mmol) in 2 mL dichloromethane. To this solution was added 1 mL of trifluoroacetic acid. The reaction was continued at room temperature for 45 min. The solvent was evaporated in vacuo to an oil. The crude material was purified on flash grade silica gel eluting with 50% ethyl acetate in hexane. Fractions containing the product were combined, evaporated 25 in vacuo and dried under high vacuum to provide (3*R*, 3*aS*, 6*aR*) Hexahydrofuro[2, 3*b*]furan-3-yl-*N*-(1*S*, 2*R*)-1-benzyl-3-[(cyclopentyloxy)[(3-*N*-methylphenyl) sulfonyl]amino-2-hydroxypropyl carbamate (17.1 mg, 93%). HPLC showed the material to be 98% pure; Ret. time = 11.0 30 min.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 7.12-7.35 (m, 9H), 5.60 (m, 1H), 4.75-5.10 (m, 3H), 3.70-3.91 (m, 6H), 3.54 (m, 2H), 3.29 (m, 1H), 2.84-3.09 (m, 7H), 1.18-1.98 (m, 9H) and LCMS (ES+), M $^+$ H = 590.2.

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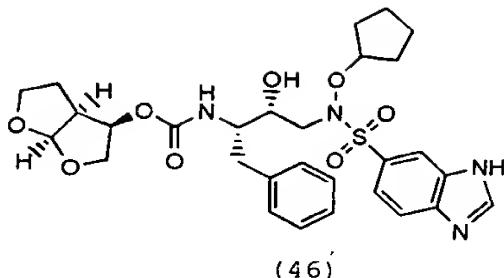
Example 46

## Step 1



5 ***N*-[(2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl]-*N*-(cyclopentyloxy)-1*H*-benzimidazole-6-sulfonamide.** A mixture of tert-butyl *N*-(1*S*,2*R*)-3-[(1*H*-benzimidazol-6-ylsulfonyl)(cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate (Example 82), (0.500 g, 0.919 mmol) 10 and trifluoroacetic acid (5mL) was stirred under an Argon atmosphere at ambient temperature for approximately one hour. The reaction was evaporated *in vacuo* and the residue was partitioned between 1N aqueous sodium hydroxide and dichloromethane. After separating the layers, the aqueous 15 phase was diluted with saturated aqueous brine and extracted three times with dichloromethane followed by two extractions with ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, evaporated *in vacuo* and dried under high vacuum to provide *N*-[(2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl]-*N*-(cyclopentyloxy)-1*H*-benzimidazole-20 6-sulfonamide (0.423 g, 104%). *H*1-NMR (chloroform-D3): 1.60 (m, 4H), 1.84 (m, 4H), 2.52 (m, 4H), 2.90 (m, 1H), 3.03 (m, 1H), 3.27(m, 2H), 3.86 (m, 1H), 4.90 (m, 1H), 7.25(m, 6H), 7.81(m, 2H), 8027(m, 2H). MS(ESI): 445 (M+H).  
25

## Step 2:

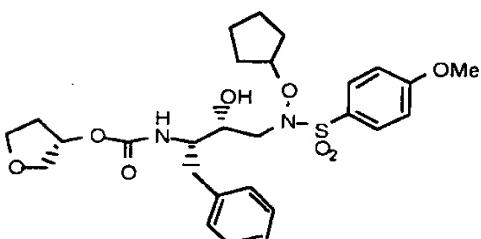


(3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(1*H*-benzimidazol-6-ylsulfonyl)(cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate. A mixture of (2*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-2-yl 4-nitrophenyl carbonate (38.3 mg, 0.124 mmol) and imidazole (15 mg, 0.222 mmol) were heated under Argon in approximately 2 mL of acetonitrile for 1.5 hrs. To this mixture was then added (*N*-[(2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl]-*N*-(cyclopentyloxy)-1*H*-benzimidazole-6-sulfonamide (50 mg, 0.113 mmol) and *N,N*-diisopropylethylamine (58.9  $\mu$ L, 0.338 mmol). After heating at reflux for an additional 6 hrs., the reaction was cooled and evaporated *in vacuo*. The residue was dissolved in ethyl acetate, washed three times with 5% aqueous potassium carbonate, washed with brine, dried over anhydrous sodium sulfated, filtered and evaporated *in vacuo*. The residue was purified on a preparative TLC plate (20X20 cm, 1000  $\mu$ M) eluting with 95:5 methylene chloride : methanol. The plate was allowed to dry through evaporation and then eluted again with 93:7 chloroform : methanol. The product band was removed, eluted with 4:1 methylene chloride : methanol, filtered, and evaporated *in vacuo*. The residue was lyophilized from acetonitrile : water to provide (3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(1*H*-benzimidazol-6-ylsulfonyl)(cyclopentyloxy)amino]-1-benzyl-2-

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hydroxypropylcarbamate (25 mg, 37%). <sup>1</sup>H-NMR (dimethylsulfoxide-D6): 1.05 (m, 1H), 1.27 (m, 1H), 1.58 (m, 8H), 2.33 (m, 1H), 2.64 (m, 2H), 2.96 (m, 2H), 3.45 (m, 4H), 3.62 (m, 2H), 4.72 (m, 2H), 5.16 (m, 1H), 5.42 (d, 1H), 5 7.10 (m, 6H), 7.51 (m, 1H), 7.72 (m, 1H), 7.93 (m, 1H); 8.44 (s, 1H), 13.0 (b, 1H). MS (ESI): 601 (M+H).

Example 47



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(47)

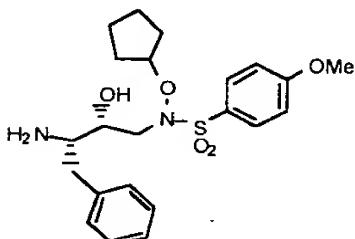
**3S)-tetrahydro-3-furanyl N-((1S,2R)-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate.** A mixture of 2,5-dioxo-1-pyrrolidinyl [(3S)-tetrahydro-3-furanyl] carbonate (13.8 mg, 0.0602 mmol, WO94/05639), *N*<sup>1</sup>-[(2R,3S)-3-amino-2-hydroxy-4-phenylbutyl]-*N*<sup>1</sup>-(cyclopentyloxy)-4-methoxy-1-benzenesulfonamide x trifluoracetic acid (Step 1, Example 48), (30 mg, 0.0547 mmol), and *N,N*-diisopropylethylamine (23.8  $\mu$ L, 0.137 mmol) were combined at ambient temperature under an Argon atmosphere. After stirring for 18 hours, the reaction mixture was evaporated *in vacuo* to a residue and purified on a preparative silica gel TLC plate (20x20 cm, 25 500  $\mu$ M) eluting with 96:4 chloroform : methanol. The product band was removed, eluted with 3:1 methylene chloride : methanol, filtered, evaporated *in vacuo* and dried under high vacuum to provide (3S)-tetrahydro-3-furanyl *N*-(1S,2R)-

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10 1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl carbamate (26 mg, 87%) as a foam.  $^1\text{H-NMR}$  (chloroform-D3): 1.73 (m, 9H), 2.14 (m, 1H), 2.92 (m, 5H), 3.77 (m, 6H), 3.87 (s, 3H), 4.79 (bm, 2H), 5.10 (bs, 1H), 6.97 (d, 2H), 7.23 (m, 5H), 7.70 (d, 2H). MS(ESI): 571 (M+Na).

Example 48

Step 1:



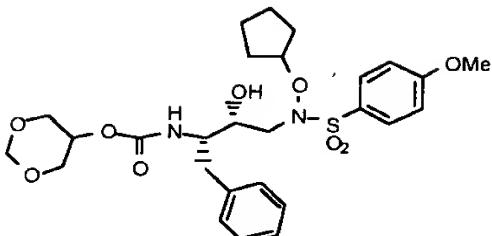
10

15  $N^1$ -[(2R,3S)-3-amino-2-hydroxy-4-phenylbutyl]- $N^1$ -trifluoracetic acid. Tert-butyl  $N$ -(1S,2R)-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl) sulfonyl]amino-2-hydroxypropyl carbamate (0.693 g, 1.29 mmol) was combined with trifluoroacetic acid (5 mL) under an Argon atmosphere at ambient temperature. After stirring for 20 minutes, the reaction mixture was evaporated *in vacuo*. The residue was dissolved several times in dichloromethane and evaporated to remove excess trifluoroacetic acid. The crude product was triturated with hexane and then evaporated and dried under high vacuum to provide the trifluoroacetic acid salt of  $N^1$ -[(2R,3S)-3-amino-2-hydroxy-4-phenylbutyl]- $N^1$ -trifluoracetic acid (0.769g, 108%).  $^1\text{H-NMR}$  (chloroform-D3 + NaOD): 1.58 (m, 4H), 1.78 (m, 4H), 2.45 (m, 1H), 2.85 (m, 1H), 2.96 (m, 1H), 3.15 (m, 1H), 3.22 (m, 1H), 3.77 (m, 1H), 3.88 (s, 3H), 4.78 (m, 1H),

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7.00 (m, 2H), 7.23 (m, 5H), 7.78 (m, 2H). MS (ESI): 435 (MH<sup>+</sup>).

Step 2:



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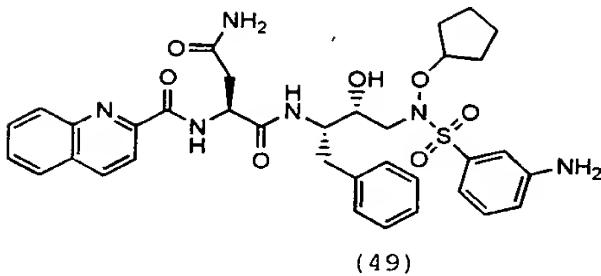
1,3-dioxolan-5-yl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate. A  
 10 mixture of 1,3-dioxolan-5-yl (4-nitrophenyl) carbonate [16.2 mg, 0.0602 mmol, Application: WO 96-US5473], *N*<sup>1</sup>-[(2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl]-*N*<sup>1</sup>-(cyclopentyloxy)-4-methoxy-1-benzenesulfonamide.trifluoracetic acid (30 mg, 0.0547 mmol], and *N,N*-diisopropylethylamine (23.8  $\mu$ L, 0.137 mmol) were combined in approximately 1.5 mL acetonitrile at ambient temperature under an Argon atmosphere. After stirring for 18 hours, the reaction mixture was evaporated *in vacuo* to a residue and purified on a preparative silica gel TLC plate (20x20 cm, 500  $\mu$ M) eluting with 96:4  
 15 chloroform : methanol. The product band was removed, eluted with 3:1 methylene chloride : methanol, filtered, and evaporated *in vacuo*. The residue was dissolved in diethylether, evaporated *in vacuo* and dried under high vacuum to provide 1,3-dioxolan-5-yl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate (20.6 mg, 67%) as a foam. H<sub>1</sub>-NMR (chloroform-D3): 1.66 (m, 8H), 2.94 (m, 5H), 3.87 (m, 8H),

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4.48 (bs, 1H), 4.76 (m, 2H), 4.94 (m, 2H), 6.97 (m, 2H), 7.24 (m, 5H), 7.69 (m, 2H). MS (ESI): 587 (M+Na).

Example 49

5



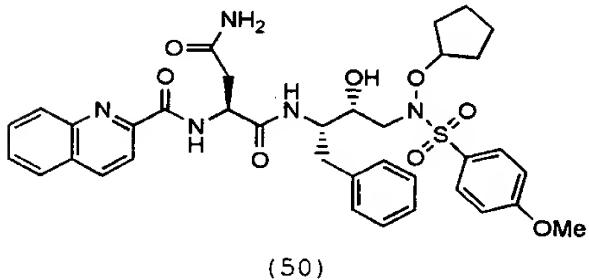
(2*S*) -*N*<sup>1</sup> - [(2*R*, 3*S*) -3-amino-2-hydroxy-4-phenylbutyl] -*N*<sup>3</sup> - [(2-quinolinyl carbonyl)amino]butanediamide. A mixture of 3-amino-*N*<sup>1</sup> - [(2*R*, 3*S*) -3-amino-2-hydroxy-4-phenylbutyl] -*N*<sup>3</sup> - (cyclopentyloxy)-1-benzenesulfonamide (Step 1, Example 27), (60 mg, 0.143), 1-(3-dimethylaminopropyl)-3-  
 10 ethylcarbodiimide hydrochloride (29 mg, 0.15 mmol), N-hydroxybenzotriazole (20 mg, 0.15 mmol), and (2*S*) -4-amino-4-oxo-2-[(2-quinolinyl carbonyl)amino]butanoic acid hydrochloride (49 mg, 0.15 mmol, Eur. Pat. Appl. EP 432694) was combined under an Argon atmosphere at ambient  
 15 temperature in anhydrous dimethylformamide (2 mL). After addition of N,N- diisopropylethylamine (76  $\mu$ L, 0.437 mmol), the mixture was stirred for 16 hours. The reaction solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate. The solution was transferred to a separatory  
 20 funnel and washed twice with 1N sodium hydrogen sulfate. The combined aqueous layers were extracted with ethyl acetate. The combined organic layers were washed with 5% aqueous potassium carbonate and brine, dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The  
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residue was purified on a preparative TLC plate (20X20 cm, 1000  $\mu$ M) eluting with 95:5 methylene chloride : methanol. The product band was removed, eluted with 3:1 methylene chloride : methanol, filtered, and evaporated *in vacuo*. The 5 residue was purified again on a preparative TLC plate (20X20 cm, 500  $\mu$ M) eluting with 95:5 methylene chloride : methanol. The product band was removed, eluted with 3:1 methylene chloride : methanol, filtered, and evaporated *in vacuo*. The residue was lyophilized from acetonitrile : water to provide 10 (2S)-N<sup>1</sup>-(1S,2R)-3-[(3-aminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropyl-2-[(2-quinolinylcarbonyl)amino]butanediamide (32 mg, 33%) as a white lyophile. <sup>1</sup>H-NMR (chloroform-D3): 1.57 (m, 8H), 2.57 (m, 1H), 2.82 (m, 4H), 3.09 (m, 1H), 3.35 (b, 1H), 3.73 (b, 1H), 4.18 (m, 3H), 4.74 15 (m, 1H), 4.87 (m, 1H), 5.47 (b, 1H), 5.86 (b, 1H), 7.00 (m, 10H), 7.56 (m, 1H), 7.73 (m, 1H), 7.81 (d, 1H), 8.11 (m, 2H), 8.24 (d, 1H), 9.15 (d, 1H). MS(ESI): 689(M+H).

Example 50

20



(2S)-N<sup>1</sup>-((1S,2R)-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)-2-[(2-quinolinylcarbonyl)amino]butanediamide. A mixture of N<sup>1</sup>-[(2R,3S)-3-amino-2-hydroxy-4-phenylbutyl]-N<sup>1</sup>-(cyclopentyloxy)-4-methoxy-1-benzenesulfonamide (Step 1, Example 48), (73 mg, 0.168), 1-(3-dimethylaminopropyl)-3-

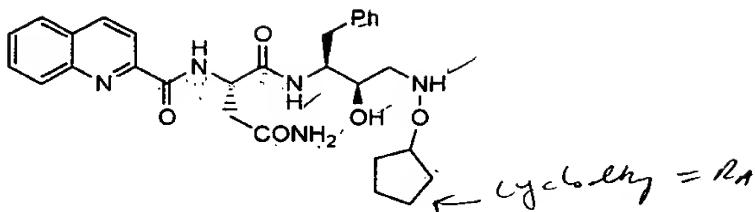
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ethylcarbodiimide hydrochloride (34 mg, 0.18 mmol), N-hydroxybenzotriazole (24 mg, 0.18 mmol), and (2S)-4-amino-4-oxo-2-[(2-quinolinylcarbonyl) amino]butanoic acid hydrochloride (57 mg, 0.18 mmol, Eur. Pat. Appl. EP 432694) 5 was combined under an Argon atmosphere at ambient temperature in anhydrous dimethylformamide (2 mL). After addition of N,N-diisopropylethylamine (896  $\mu$ L, 0.513 mmol), the mixture was stirred for 16 hours. The reaction solvent was removed *in vacuo* and the residue was dissolved in ethyl 10 acetate. The solution was transferred to a separatory funnel and washed twice with 1N sodium hydrogen sulfate. The combined aqueous layers were extracted with ethyl acetate. The combined organic layers were washed with 5% aqueous potassium carbonate and brine, dried over anhydrous 15 magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified on a preparative TLC plate (20X20 cm, 1000  $\mu$ M) eluting with 97:3 chloroform : methanol. The product band was removed, eluted with 3:1 methylene chloride : methanol, filtered, and evaporated *in vacuo*. The residue 20 was triturated with hexane and diethyl ether. The slurry was evaporated *in vacuo* to a residue and dried under high vacuum to provide (2S)-N<sup>1</sup>-((1S,2R)-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)-2-[(2-quinolinylcarbonyl)amino]butanediamide 25 (49 mg, 41%) as a white solid. H<sub>1</sub>-NMR (chloroform-D3): 1.52 (m, 4H), 1.75 (m, 4H), 2.82 (m, 5H), 3.10 (m, 1H), 3.82 (b, 1H), 3.84 (s, 3H), 3.91 (m, 1H), 4.29 (m, 1H), 4.78 (m, 1H), 4.95 (m, 1H), 5.76 (b, 1H), 6.22 (b, 1H), 7.00 (m, 5H), 7.12 (d, 2H), 7.22 (d, 1H), 7.60 (m, 1H), 7.75 (m, 3H), 7.83 (d, 30 1H), 8.14 (m, 2H), 8.25 (d, 1H), 9.15 (d, 1H). MS (ESI): 704 (M+H).

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Example 51

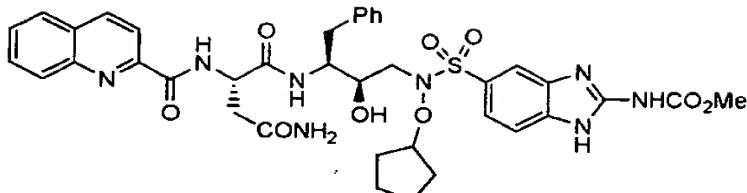
Step 1:



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(2S)-4-Amino-4-oxo-2-[(2-quinolinylcarbonyl)amino]butanamido N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)amino]-2-hydroxypropylcarbamate. Tert-butyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)amino]-2-hydroxypropylcarbamate (412 mg, 1.13 mmol) was dissolved in dichloromethane (8 mL) in a 25 mL round bottomed flask under nitrogen and trifluoroacetic acid (4 mL) was added slowly. After the solution was stirred for 4 hours, TLC indicated loss of starting material. After the workup described in Step 2, Example 54, the residue was dissolved in anhydrous DMF (5 mL) followed by (2S)-4-amino-4-oxo-2-[(2-quinolinylcarbonyl)amino]butanoic acid hydrochloride (320 mg, 1.13 mmol), anhydrous diisopropylethylamine (0.4 mL, 2.26 mmol), 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride (220 mg, 1.13 mmol), and 1-hydroxy-benzotriazole (150 mg, 1.13 mmol). The reaction was stirred for 18 h and concentrated in vacuo. Ethyl acetate (15 mL) and 1N HCl (15 mL) were added and the layers were separated. The aqueous layer was adjusted with solid sodium carbonate to pH 9 and then extracted with ethyl acetate (25 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. Preparative silica gel TLC of the residue using 90:10 chloroform: methanol as eluent yielded the product as a white solid (91 mg, 0.171 mmol, 15%). MS(ES): 534 (M+1), 30 532 (M-1).

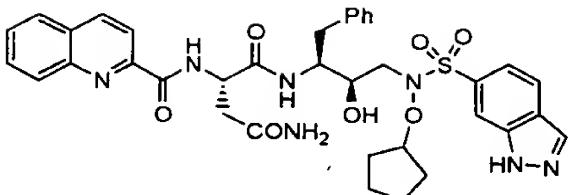
Step 2:



(51)

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(2*S*)-4-Amino-4-oxo-2-[(2-quinolinylcarbonyl)amino]butanamido N-(1*S*,2*R*)-1-benzyl-3-[(cyclopentyloxy)(2-  
 { (methoxycarbonyl)amino}-1*H*-benzimidazol-5-  
 ylsulfonyl)amino]-2-hydroxypropylcarbamate. (2*S*)-4-Amino-4-  
 10 oxo-2-[(2-quinolinylcarbonyl)amino]butanamido N-(1*S*,2*R*)-1-  
 benzyl-3-[(cyclopentyloxy)-amino]-2-hydroxypropylcarbamate  
 (Step 1, above), (44 mg, 0.0825 mmol), methyl N-[5-  
 15 (chlorosulfonyl)-1*H*-benzimidazol-2-yl]carbamate (24 mg,  
 0.0825 mmol), and anhydrous diisopropylethylamine (0.05 mL,  
 0.280 mmol) were combined in anhydrous tetrahydrofuran (3  
 mL) in a 25 mL round bottomed flask under nitrogen. The  
 reaction was stirred for 24 hours and concentrated in vacuo.  
 Ethyl acetate (30 mL) and water (10 mL) were added and the  
 layers were separated. The organic layer was washed with  
 20 brine (10 mL), dried over anhydrous sodium sulfate,  
 filtered, and concentrated in vacuo. The residue was  
 purified by preparative silica gel TLC using 90:10  
 chloroform: methanol as an eluent to provide the desired  
 product as a white solid (11 mg, 0.014 mmol, 17%). <sup>1</sup>HNMR  
 25 (d<sub>6</sub>-DMSO) δ: 8.86 (d, J=8.4 Hz, 1H), 8.62 (d, J=8.4 Hz,  
 1H), 8.22-6.94 (m, 12H), 5.19 (d, J=6.2 Hz, 1H), 4.77-4.72  
 (m, 2H), 4.02-1.35 (m, 17H), 3.80 (s, 3H). MS (ES): 787  
 (M+1), 785 (M-1).

Example 52

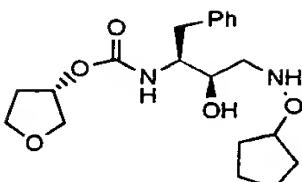
(52)

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(2S)-4-Amino-4-oxo-2-[(2-quinolinylcarbonyl)amino]butanamido N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)-2-hydroxypropyl]carbamate. (2S)-4-Amino-4-oxo-2-[(2-quinolinylcarbonyl)-amino]butanamido N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)-amino]-2-hydroxypropylcarbamate (Step 1, Example 51), (44 mg, 0.0825 mmol), 1-trityl-1H-indazole-6-sulfonyl chloride (38 mg, 0.0825 mmol), and anhydrous diisopropylethylamine (0.05 mL, 0.280 mmol) were combined in anhydrous tetrahydrofuran (3 mL) in a 25 mL round bottomed flask under nitrogen. The reaction was stirred for 24 hours and concentrated in vacuo. Ethyl acetate (30 mL) and water (10 mL) were added and the layers were separated. The organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The compound was deprotected as described in Example 57 and purified by preparative silica gel TLC using 90:10 chloroform: methanol as an eluent to provide the desired product as a white film (9 mg, 0.013 mmol, 15%).  $^1\text{H}$ NMR ( $d_6$ -DMSO)  $\delta$ : 8.84 (d,  $J=8.5$  Hz, 1H), 8.61 (d,  $J=8.5$  Hz, 1H), 8.31-6.95 (m, 13H), 5.24 (d,  $J=6.6$  Hz, 1H), 4.81-4.72 (m, 2H), 3.97 (bs, 1H), 3.68 (bs, 1H), 3.40-1.20 (m, 15H). MS(ES): 714 (M+1), 712 (M-1).

Example 53

Step 1:

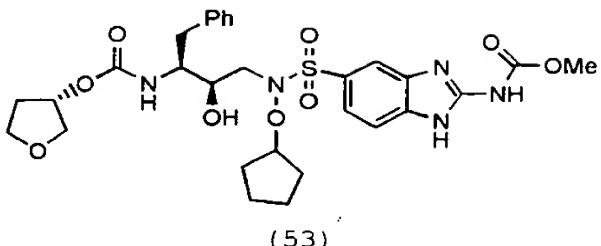


5

(3S) Tetrahydro-3-furanyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)amino]-2-hydroxypropylcarbamate. Tert-butyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)amino]-2-hydroxypropylcarbamate [Example 54] (1.05 g, 2.88 mmol) was dissolved in dichloromethane (12 mL) in a 50 mL round bottomed flask under nitrogen and trifluoroacetic acid (8 mL) was added slowly. After the solution was stirred for 4 hours, TLC indicated loss of starting material. After the workup described in Step 2, Example 54, the residue was dissolved in anhydrous acetonitrile (15 mL), followed by 1-((3S)tetrahydro-3-furanyloxy)-carbonyloxy)dihydro-1*H*-pyrrole-2,5-dione (660 mg, 2.88 mmol), anhydrous diisopropylethylamine (0.50 mL, 2.88 mmol), and N,N-dimethylaminopyridine (105 mg, 0.86 mmol). The reaction was heated at 50°C for 2 hours, allowed to cool, and concentrated in vacuo. After the workup described in Step 2, Example 54, the residue was purified by flush chromatography over a bed of silica gel using a gradient elution of hexane: ethyl acetate (1:2 to 1:5) to give the desired product as a white foam (440 mg, 1.16 mmol, 40%). MS(ES): 379 (M+1).

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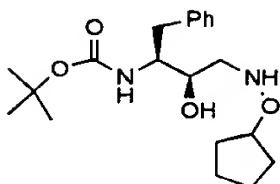
Step 2:



5 (3S) Tetrahydro-3-furanyl N-(1S,2R)-1-benzyl-3-  
 [(cyclopentyloxy) (2-[(methoxycarbonyl) amino]-1H-  
 benzimidazol-5-ylsulfonyl) amino]-2-hydroxypropylcarbamate.  
 (3S) Tetrahydro-3-furanyl N-(1S,2R)-1-benzyl-3-  
 [(cyclopentyloxy) amino]-2-hydroxypropylcarbamate (120 mg,  
 10 0.317 mmol), methyl N-[5-(chlorosulfonyl)-1H-benzimidazol-2-  
 yl]carbamate (100 mg, 0.345 mmol), anhydrous  
 diisopropylethylamine (0.06 mL, 0.345 mmol), and N,N-  
 dimethylaminopyridine (12 mg, 0.09 mmol) were combined in  
 anhydrous tetrahydrofuran (6 mL) and anhydrous N,N-  
 15 dimethylformamide (3 mL) in a 25 mL round bottomed flask  
 under nitrogen. The reaction was stirred for 24 hours and  
 concentrated in vacuo. After the workup described in Step  
 3, Example 54, the residue was purified by preparative  
 silica gel TLC using 90:10 chloroform: methanol as an eluent  
 20 to provide the desired product as a colorless glass (43 mg,  
 0.068 mmol, 21%).  $^1\text{H}$ NMR ( $d_6$ -DMSO)  $\delta$ : 7.96-7.08 (m, 10H),  
 5.19 (d,  $J=6.7$  Hz, 1H), 4.96-4.82 (m, 3H), 3.81 (s, 3H),  
 3.75-3.40 (m, 6H), 3.09-2.40 (m, 4H), 2.09-1.35 (m, 8H).  
 MS(ES): 632 (M+1), 630 (M-1).

Example 54

Step 1:



5

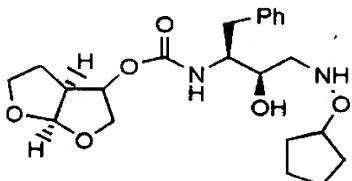
**Tert-butyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)amino]-2-hydroxypropylcarbamate.** To a solution of 2-(cyclopentyloxy)-1H-isoindole-1,3(2H)-dione (11.3 g, 48.9 mmol) in anhydrous tetrahydrofuran (60 mL) in a 200 mL round bottomed flask under nitrogen was added anhydrous hydrazine (1.6 g, 48.9 mmol) dropwise via syringe. The resulting thick white slurry was vigorously stirred for 2.5 hours and then filtered through a fritted funnel. The cake was washed with tetrahydrofuran (2 x 20 mL) and the combined filtrates were placed in a 300 mL round bottomed flask under nitrogen and equipped with a condenser. Tert-butyl N-(1S)-1-[(2S)oxiranyl]-2-phenylethylcarbamate (7.50 g, 28.5 mmol) was added along with anhydrous lithium triflate (6.20 g, 39.7 mmol) and the reaction was heated at reflux for 24 hours. The reaction was allowed to cool and was concentrated in vacuo to a viscous oil. Diethyl ether (150 mL) and water (50 mL) were added and the layers were separated. The ethereal layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Flush chromatography over a bed of silica gel using a gradient elution of hexane: ethyl acetate (4:1 to 2:1) gave the desired product as a white solid (8.90 g, 24.4 mmol, 86% based upon starting epoxide).  $^1\text{H}$ NMR ( $\text{CDCl}_3$ )  $\delta$ : 7.32-7.19 (m, 5H), 5.90 (bs, 1H), 4.59 (d,  $J=8.1$  Hz, 1H), 4.24-4.20

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(m, 1H), 3.90-3.58 (m, 3H), 3.16-2.83 (m, 4H), 1.69-1.35 (m, 16H) MS (ES): 365 (M+1), 265 (M-BOC).

Step 2:

5



(3aS,6aR) Hexahydrofuro[2,3-b]furan-3-yl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)amino]-2-hydroxypropylcarbamate. Tert-  
10 butyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)amino]-2-  
hydroxy-propylcarbamate (step 1 above), (1.50 g, 4.12 mmol)  
was dissolved in dichloromethane (15 mL) in a 50 mL round  
bottomed flask under nitrogen and trifluoroacetic acid (10  
mL) was added slowly. After the solution was stirred for 3  
15 hours, TLC indicated loss of starting material. The  
reaction was concentrated in vacuo and ethyl acetate (30 mL)  
was added. A 10% solution of aqueous sodium carbonate was  
added portionwise until the pH was adjusted to 9. The  
layers were separated and the organic layer was extracted  
20 with 1 N HCl (20 mL). The aqueous layer was then neutralized  
with solid sodium carbonate until the pH was 9. The  
resulting white precipitate was dissolved by the addition of  
ethyl acetate (100 mL) and the layers were separated. The  
aqueous layer was extracted with ethyl acetate (25 mL) and  
25 the combined organic layers were dried over anhydrous sodium  
sulfate, filtered, and concentrated in vacuo to a sticky  
white solid. Anhydrous acetonitrile (20 mL) was added,  
followed by racemic (3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl  
4-nitrophenyl carbonate (1.21 g, 4.12 mmol), anhydrous  
30 diisopropylethylamine (0.72 mL, 4.12 mmol), and N,N-

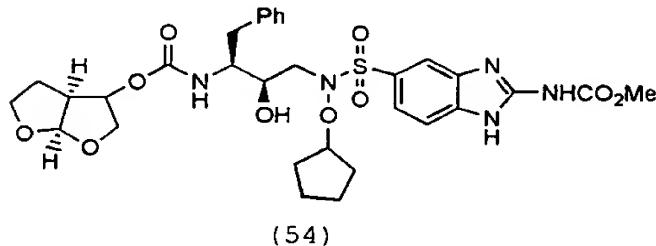
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dimethylaminopyridine (150 mg, 1.23 mmol). The reaction was heated at 50°C for 2 hours, allowed to cool, and concentrated in vacuo. Diethyl ether (50 mL) and 5% sodium carbonate (20 mL) were added and the layers were separated.

5 The organic layer was washed with water (20 mL), brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Flash chromatography over a bed of silica gel using a gradient elution of hexane: ethyl acetate (1:1 to 1:4) gave the desired product as a pale yellow foam

10 (1.41 g, 33.5 mol, 81%).  $^1\text{H}$ NMR ( $\text{d}_6$ -DMSO):  $\delta$  7.29-7.13 (m, 5H), 6.18 (bs, 1H), 5.58-5.52 (m, 1H), 4.96-4.82 (m, 2H), 4.14 (bs, 1H), 3.88-3.34 (m, 6H), 3.04-2.53 (m, 6H), 1.92-1.30 (m, 9H). MS (ES): 421 (M+1), 419 (M-1).

15 Step 3:

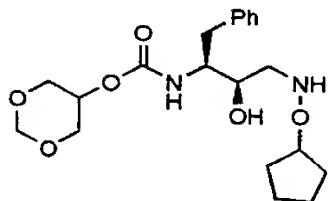


(3aS,6aR) Hexahydrofuro[2,3-b]furan-3-yl N-(1S,2R)-1-benzyl-  
20 3-[(cyclopentyloxy)(2-[(methoxycarbonyl)amino]-1H-benzimidazol-5-ylsulfonyl)amino]-2-hydroxypropylcarbamate.  
(3aS,6aR) Hexahydrofuro[2,3-b]furan-3-yl N-(1S,2R)-1-benzyl-  
3-[(cyclopentyloxy)amino]-2-hydroxypropylcarbamate (100 mg, 0.238 mmol), methyl N-[5-(chlorosulfonyl)-1H-benzimidazol-2-  
25 yl]carbamate (70 mg, 0.238 mmol), anhydrous diisopropylethylamine (0.04 mL, 0.238 mmol), and N,N-dimethylamino-pyridine (9 mg, 0.07 mmol) were combined in anhydrous tetrahydrofuran (5 mL) and anhydrous N,N-dimethylformamide (3 mL) in a 25 mL round bottomed flask  
30 under nitrogen. The reaction was stirred for 24 hours and

concentrated in vacuo. Ethyl acetate (30 mL) and 0.5 N HCl (10 mL) were added and the layers were separated. The organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Preparative silica gel TLC using 90:10 chloroform: methanol as an eluent provided the product as a white foam (83 mg, 0.123 mmol, 52%).  $^1\text{H}$ NMR ( $\text{d}_6$ -DMSO)  $\delta$ : 7.60-7.15 (m, 10H), 5.51-5.46 (m, 1H), 5.21 (bd,  $J=5.9$  Hz, 1H), 4.82-4.69 (m, 2H), 3.81 (s, 3H), 3.78-3.57 (m, 8H), 3.19-2.42 (m, 4H), 2.02-1.30 (m, 8H). MS(ES): 674 (M+1), 672 (M-1).

Example 55

Step 1:



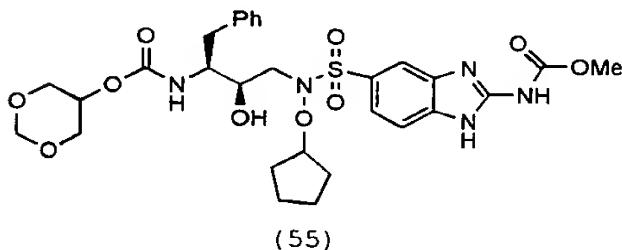
1,3-Dioxan-5-yl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)amino]-2-hydroxypropylcarbamate. Tert-butyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)amino]-2-

20 hydroxypropylcarbamate (1.38 g, 3.79 mmol) was dissolved in dichloromethane (15 mL) in a 50 mL round bottomed flask under nitrogen and trifluoroacetic acid (8 mL) was added slowly. After the solution was stirred for 4 hours, TLC indicated loss of starting material. After the workup 25 described in Step 2, Example 54, the residue was dissolved in anhydrous acetonitrile (20 mL), followed by 1,3-dioxan-5-yl 4-nitrophenyl carbonate (1.02 g, 3.79 mmol), anhydrous diisopropylethylamine (0.65 mL, 3.8 mmol), and N,N-dimethylaminopyridine (140 mg, 1.14 mmol). The reaction was 30 heated at 50°C for 2 hours, allowed to cool, and

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concentrated in vacuo. After the workup described in Step 2, Example 54, the residue was purified by flush chromatography over a bed of silica gel using a gradient elution of hexane: ethyl acetate (1:2 to 1:4) to give the 5 desired product as a white foam (600 mg, 1.52 mmol, 40%).  
<sup>1</sup>HNMR (d<sub>6</sub>-DMSO) δ: 7.30-7.17 (m, 5H), 6.15 (bs, 1H), 4.91-4.67 (m, 3H), 4.35-3.50 (m, 4H), 3.11-2.52 (m, 8H), 1.68-1.36 (m, 8H). MS (ES): 395 (M+1).

10 Step 2:



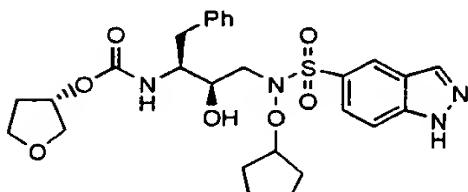
15 1,3-Dioxan-5-yl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)(2-((methoxycarbonyl)amino)-1H-benzimidazol-5-ylsulfonyl)amino]-2-hydroxypropylcarbamate. 1,3-Dioxan-5-yl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)-amino]-2-hydroxypropylcarbamate (Step 1, above), (100 mg, 0.254 mmol), methyl N-[5-(chlorosulfonyl)-1H-benzimidazol-2-yl]carbamate (73 mg, 0.254 mmol), anhydrous diisopropylethyl-amine (0.05 mL, 0.254 mmol), and N,N-dimethylaminopyridine (9 mg, 0.08 mmol) were combined in anhydrous tetrahydrofuran (5 mL) and anhydrous N,N-dimethylformamide (2 mL) in a 25 mL round bottomed flask under nitrogen. The reaction was stirred for 24 hours and concentrated in vacuo. After the workup described in Step 3, Example 54, the residue was purified by preparative silica gel TLC using 93:7 chloroform: methanol as an eluent 20 to provide the desired product as a colorless glass (40 mg, 25

30

0.0618 mmol, 24%).  $^1\text{H}$ NMR ( $\text{d}_6$ -DMSO)  $\delta$ : 7.96-7.16 (m, 10H), 5.17 (d,  $J=6.4$  Hz, 1H), 4.82-4.65 (m, 3H), 4.26 (bs, 1H), 3.81 (s, 3H), 3.78-3.49 (m, 5H), 3.05-2.40 (m, 4H), 2.05-1.40 (m, 8H). MS(ES): 648 (M+1), 646 (M-1).

5

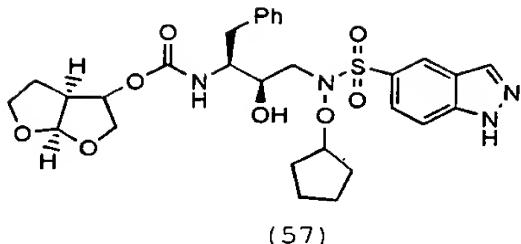
Example 56



(56)

10

(3S) Tetrahydro-3-furanyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)(1H-indazol-5-ylsulfonyl)amino]-2-hydroxypropylcarbamate. (3S) Tetrahydro-3-furanyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)amino]-2-hydroxypropylcarbamate (Step 1, Example 53), (90 mg, 0.238 mmol), 1-trityl-1H-indazole-5-sulfonyl chloride (110 mg, 0.238 mmol), anhydrous diisopropylethylamine (0.04 mL, 0.238 mmol), and N,N-dimethylaminopyridine (9 mg, 0.07 mmol) were combined in anhydrous tetrahydrofuran (4 mL) in a 25 mL round bottomed flask under nitrogen. The reaction was stirred for 24 hours and concentrated in vacuo. After the workup described in Step 3, Example 54, the residue was purified by preparative silica gel TLC using 1:1 hexane: ethyl acetate as an eluent to give the tritylated product as a colorless film. The compound was deprotected as described in Example 57 and purified by preparative silica gel TLC using 3:1 ethyl acetate: hexane as an eluent to provide the desired product as a colorless film (6 mg, 0.01 mmol, 5%). (no HNMR data available). MS(ES): 559 (M+1), 557 (M-1).

Example 57

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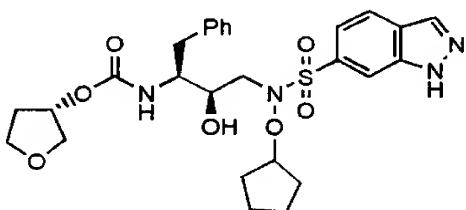
**(3aS,6aR) Hexahydrofuro[2,3-b]furan-3-yl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)(1H-indazol-5-ylsulfonyl)amino]-2-hydroxypropylcarbamate.** (3aS,6aR) Hexahydrofuro[2,3-b]furan-3-yl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)-amino]-2-hydroxy

10 propylcarbamate (100 mg, 0.238 mmol) (Step 2, Example 54), 1-trityl-1H-indazole-5-sulfonyl chloride (110 mg, 0.238 mmol), anhydrous diisopropylethylamine (0.04 mL, 0.238 mmol), and N,N-dimethylaminopyridine (9 mg, 0.07 mmol) were combined in anhydrous tetrahydrofuran (5 mL) in a 25 mL 15 round bottomed flask under nitrogen. The reaction was stirred for 24 hours and concentrated in vacuo. After the workup described in Step 3, Example 54, the residue was purified by preparative silica gel TLC using 1:1 hexane: ethyl acetate as an eluent to give the tritylated product as 20 a colorless film (80 mg, 0.095 mmol, 40%). The trityl protecting group was removed by dissolving the compound in dichloromethane (3 mL) and adding trifluoroacetic acid (1 mL). After 2.5 hours of stirring, the reaction was concentrated in vacuo. Ethyl acetate (15 mL) and 10% 25 aqueous sodium carbonate (5 mL) were added and the layers separated. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by preparative silica gel TLC using 3:1 ethyl acetate: hexane as an eluent to provide the desired 30 product as a white solid (30 mg, 0.05 mmol, 53%).  $^1\text{H}$ NMR

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(d<sub>6</sub>-DMSO) δ: 8.39-8.30 (m, 2H), 7.81-7.67 (m, 2H), 7.25-7.17 (m, 5H), 5.51-5.46 (m, 1H), 5.25 (d, J=6.3 Hz, 1H), 4.83-4.62 (m, 2H), 4.14-4.12 (m, 4H), 3.72-1.26 (m, 18H).  
 MS (ES): 601 (M+1), 599 (M-1).

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Example 58

(58)

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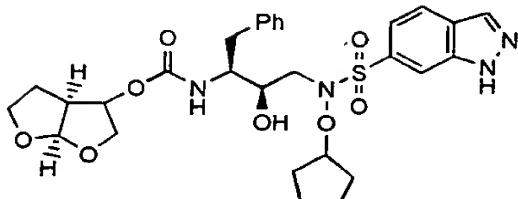
(3S) Tetrahydro-3-furanyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)(1H-indazol-6-ylsulfonyl)amino]-2-hydroxypropylcarbamate. (3S) Tetrahydro-3-furanyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)amino]-2-hydroxypropylcarbamate (Step 1, Example 53), (120 mg, 0.317 mmol), 1-trityl-1H-indazole-6-sulfonyl chloride (146 mg, 0.317 mmol), anhydrous diisopropylethylamine (0.06 mL, 0.317 mmol), and N,N-dimethylaminopyridine (12 mg, 0.1 mmol) were combined in anhydrous tetrahydrofuran (5 mL) in a 25 mL round bottomed flask under nitrogen. The reaction was stirred for 24 hours and concentrated in vacuo. After the workup described in Step 3, Example 54, the residue was purified by preparative silica gel TLC using 1:1 hexane: ethyl acetate as an eluent to give the tritylated product as a colorless film (100 mg, 0.125 mmol). The compound was deprotected as described in Example 57 and purified by preparative silica gel TLC using 3:1 ethyl acetate: hexane as an eluent to provide the desired product as a colorless glass (30 mg, 0.0537 mmol, 43%). <sup>1</sup>HNMR (d<sub>6</sub>-DMSO) δ: 8.33 (bs, 1H), 8.07-8.00 (m, 2H),

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7.49-7.41 (m, 1H), 7.26-7.08 (m, 5H), 5.32-4.78 (m, 4H), 3.81-1.25 (m, 20H). MS(ES): 559 (M+1), 557 (M-1).

Example 59

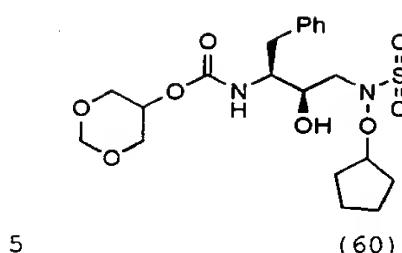
5



(59)

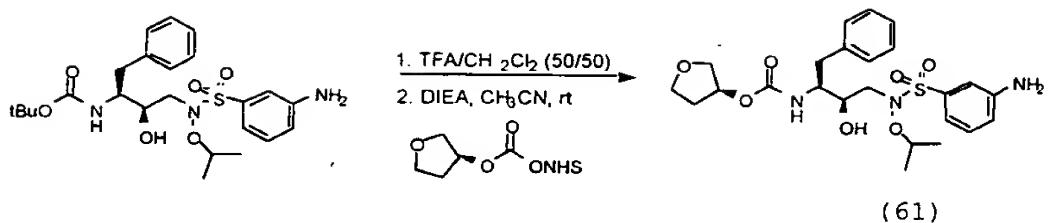
**(3aS,6aR) Hexahydro[2,3-b]furan-3-yl N-(1S,2R)-1-benzyl-3-**

**[(cyclopentyloxy) (1H-indazol-6-ylsulfonyl)amino]-2-**  
**hydroxypropylcarbamate.** (3aS,6aR) Hexahydrofuro[2,3-b]furan-  
 3-yl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)-amino]-2-  
 hydroxypropylcarbamate (Step 2, Example 54), (100 mg, 0.238  
 mmol), 1-trityl-1H-indazole-6-sulfonyl chloride (110 mg,  
 0.238 mmol), anhydrous diisopropylethylamine (0.04 mL, 0.238  
 mmol), and N,N-dimethylamino-pyridine (9 mg, 0.07 mmol) were  
 combined in anhydrous tetrahydrofuran (5 mL) in a 25 mL  
 round bottomed flask under nitrogen. The reaction was  
 stirred for 24 hours and concentrated in vacuo. After the  
 workup described in Step 3, Example 54, the residue was  
 purified by preparative silica gel TLC using 1:1 hexane:  
 ethyl acetate as an eluent to give the tritylated product as  
 a colorless film (117 mg, 0.139 mmol, 58%). The compound was  
 deprotected as described in Example 57 and purified by  
 preparative silica gel TLC using 3:1 ethyl acetate: hexane  
 as an eluent to provide the desired product as a colorless  
 film (60 mg, 0.100 mmol, 72%).  $^1\text{H}$ NMR ( $\text{d}_6$ -DMSO)  $\delta$ : 8.33 (bs,  
 1H), 8.08-7.99 (m, 2H), 7.50-7.45 (m, 1H), 7.23-7.15 (m,  
 5H), 5.51-5.45 (m, 1H), 5.26 (bd,  $J=5.9$  Hz, 1H), 4.85-4.66  
 (m, 2H), 3.77-1.14 (m, 22H). MS(ES): 601 (M+1), 599 (M-1).

Example 60

1,3-Dioxan-5-yl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)(1H-indazol-6-ylsulfonyl)amino]-2-hydroxypropylcarbamate. 1,3-Dioxan-5-yl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)amino]-2-hydroxypropylcarbamate (Step 1, Example 55), (100 mg, 0.254 mmol), 1-trityl-1H-indazole-6-sulfonyl chloride (117 mg, 0.254 mmol), anhydrous diisopropylethylamine (0.05 mL, 0.254 mmol), and N,N-dimethylaminopyridine (9 mg, 0.08 mmol) were combined in anhydrous tetrahydrofuran (5 mL) in a 25 mL round bottomed flask under nitrogen. The reaction was stirred for 24 hours and concentrated in vacuo. After the workup described in Step 3, Example 54, the residue was purified by preparative silica gel TLC using 1:1 hexane: ethyl acetate as an eluent to give the tritylated product as a beige foam. The compound was deprotected as described in Example 57 and purified by preparative silica gel TLC using 3:1 ethyl acetate: hexane as an eluent to provide the desired product as a colorless glass (53 mg, 0.0922 mmol, 36%).  $^1\text{H}$ NMR ( $d_6$ -DMSO)  $\delta$ : 8.32 (bs, 1H), 8.06-8.00 (m, 2H), 7.49-7.46 (m, 1H), 7.33-7.16 (m, 5H), 5.22 (d,  $J=6.5$  Hz, 1H), 4.85-4.66 (m, 3H), 4.23-3.00 (m, 12H), 2.01-1.43 (m, 8H). MS(ES): 575 (M+1), 573 (M-1).

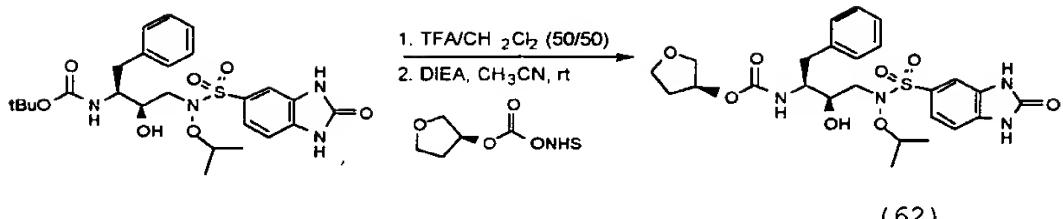
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Example 61

5 (3S) tetrahydro-3-furanyl N-(1S,2R)-3-[(3-aminophenyl)sulfonyl](isopropoxy)amino]-1-benzyl-2-hydroxypropylcarbamate. tert-Butyl N-(1S,2R)-3-[(3-aminophenyl)sulfonyl](isopropoxy)amino]-1-benzyl-2-hydroxypropylcarbamate (0.50 g, 1.01 mmol) was dissolved in TFA/CH<sub>2</sub>Cl<sub>2</sub> (50/50, 5.0 mL) at rt. After 0.5h., the TFA/CH<sub>2</sub>Cl<sub>2</sub> was removed *in vacuo* and the residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and 1.0N NaOH (50 mL). The organic layer was washed with water (1 x 25 mL), brine (1 x 25 mL), dried 10 (MgSO<sub>4</sub>), filtered, and evaporated to give the free base. To a solution of the free base in CH<sub>3</sub>CN (10 mL) was added DIEA (0.175 mL, 1.01 mmol) and 2,5-dioxo-1-pyrrolidinyl 15 [(3S)tetrahydro-3-furanyl] carbonate (0.213 g, 0.93 mmol) respectively with stirring at rt. After 1.0h., the reaction mixture was evaporated and the crude residue purified by column chromatography: 40/60 hexane/ethyl acetate to give the product as a white solid (0.320g, 63%). MS: M+NA = 530. <sup>1</sup>H NMR (CD<sub>3</sub>OD) 1.25(m, 6H); 1.80(m, 1H); 2.05(m, 1H); 2.40-3.10(m, 4H); 3.45(d, 1H); 3.75(m, 1H); 3.70-3.90(m, 5H); 20 4.50(m, 1H); 4.95(m, 1H); 6.90(d, 1H); 7.05(d, 1H); 7.10-7.35(m, 7H).

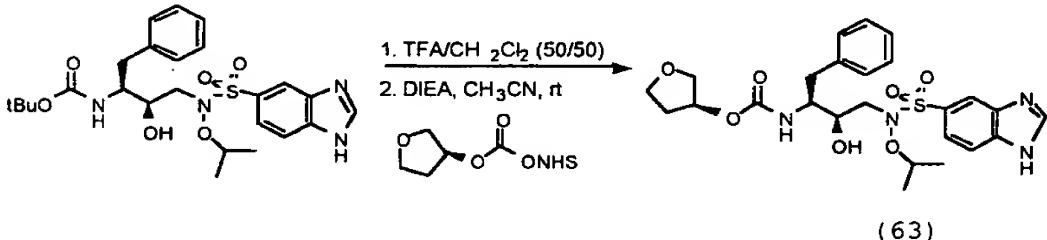
25

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Example 62

5

**(3S) tetrahydro-3-furanyl N-((1S,2R)-1-benzyl-2-hydroxy-3-isopropoxy[ (2-oxo-2,3-dihydro-1H-1,3-benzimidazol-5-yl)sulfonyl]aminopropyl)carbamate.** Prepared using the procedure outlined in Example 61. The product was purified by column chromatography: 97/3 CH<sub>2</sub>Cl<sub>2</sub>/MeOH and isolated as a white solid (40%). MS: M+H = 549 <sup>1</sup>H NMR (CD<sub>3</sub>OD) 1.25(m, 6H); 1.60(m, 1H); 1.95(m, 1H); 2.40-3.10(m, 4H); 3.40(d, 1H); 3.70-3.90(m, 5H); 4.55(m, 1H); 4.90(m, 1H); 7.20(m, 5H); 7.80(m, 2H) 8.20(s, 1H); 8.40(s, 1H) 7.20(m, 6H); 7.50(m, 2H).

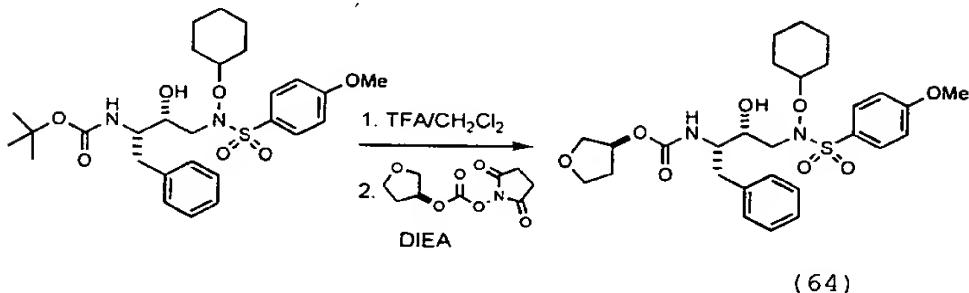
Example 63

20

**(3S) tetrahydro-3-furanyl N-(1S,2R)-3-[(1H-1,3-benzimidazol-5-ylsulfonyl) (isopropoxy)amino]-1-benzyl-2-hydroxypropylcarbamate.** Prepared using the procedure outlined in Example 6. The product was purified by column chromatography: 97/3 CH<sub>2</sub>Cl<sub>2</sub>/MeOH and isolated as white solid (31%). MS: M+H = 533 <sup>1</sup>H NMR (CD<sub>3</sub>OD) 1.25(m, 6H); 1.60(m,

1H); 1.95 (m, 1H); 2.40-3.10 (m, 4H); 3.40 (d, 1H); 3.70-3.90 (m, 5H); 4.55 (m, 1H); 4.90 (m, 1H); 7.20 (m, 5H); 7.80 (m, 2H) 8.20 (s, 1H); 8.40 (s, 1H).

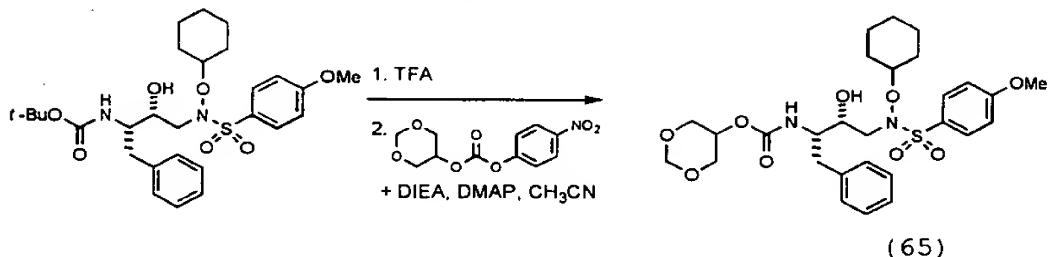
5

Example 64

10 **(3S)-tetrahydro-3-furanyl N-((1S,2R)-1-benzyl-3-(cyclohexyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate.** *tert*-butyl N-((1S,2R)-1-benzyl-3-(cyclohexyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate (0.09 mmol, 50 mg) was dissolved in 15 a 1:1 solution of CH<sub>2</sub>Cl<sub>2</sub>/TFA (1 mL) and allowed to stir at room temperature for 1 hour. The solution was then extracted into ethyl acetate, washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and concentrated to a clear oil. The resulting oil 20 was then dissolved in THF (1 mL) and combined with 2,5-dioxo-1-pyrrolidinyl [(3S)-tetrahydro-3-furanyl] carbonate (0.05 mmol, 13 mg) DIEA (0.08 mmol, 14  $\mu$ L) and allowed to stir for 15 hours. The reaction was neutralized by the addition of acetic acid and partitioned between water and 25 ethyl acetate. The organic layer was washed with saturated sodium bicarbonate and brine, and dried over magnesium sulfate. The crude product was concentrated to a white solid and purified by silica gel chromatography (1:1 hexanes/ethyl acetate), providing 19 mg (37%) of a white

solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.70 (2H, d), 7.29-7.17 (6H, m), 6.97 (2H, d), 5.1 (1H, s), 4.76 (1H, d), 4.17 (1H, m), 3.86 (3H, s), 3.87-3.70 (6H, m), 3.68-3.60 (1H, m), 3.06 (1H, bs), 2.89 (2H, m), 2.02 (3H, m), 1.89 (1H, m), 1.71 (2H, m), 1.28-1.08 (6H, m);  $\text{MS}$  (ESI):  $M+\text{Na} = 585$ .

5

Example 65

10

1,3-dioxan-5-yl  $N$ -((1*S*,2*R*)-1-benzyl-3-(cyclohexyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate.

tert-butyl  $N$ -((1*S*,2*R*)-1-benzyl-3-(cyclohexyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate (0.09 mmol, 50 mg) was stirred in 1 mL trifluoroacetic acid (TFA) at room temperature for 5 hours. The TFA was removed under vacuum, and the resulting residue was dissolved in ethyl acetate, washed with 5% aq. potassium carbonate solution, brine, dried over magnesium sulfate, and concentrated to a residue. The resulting free amine, 1,3-dioxan-5-yl 4-nitrophenyl carbonate (0.09 mmol, 25 mg), diisopropylethylamine (0.14 mmol, 0.024 mL), a crystal of  $N,N$ -dimethylaminopyridine, 4 Å molecular sieves and acetonitrile (0.5 mL) were combined and stirred at room temperature for 20 hours. The reaction solution was concentrated to a residue, dissolved in ethyl acetate, washed with 1N HCl, 5% aq. potassium carbonate solution, brine, dried over magnesium sulfate, and concentrated under vacuum. The crude residue was purified by silica gel

15

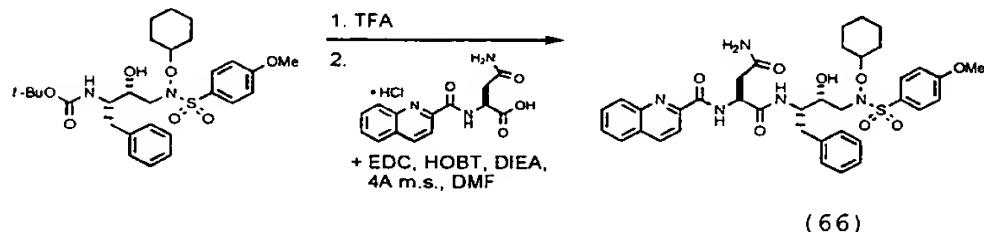
20 residue. The resulting free amine, 1,3-dioxan-5-yl 4-nitrophenyl carbonate (0.09 mmol, 25 mg), diisopropylethylamine (0.14 mmol, 0.024 mL), a crystal of  $N,N$ -dimethylaminopyridine, 4 Å molecular sieves and acetonitrile (0.5 mL) were combined and stirred at room

25 temperature for 20 hours. The reaction solution was concentrated to a residue, dissolved in ethyl acetate, washed with 1N HCl, 5% aq. potassium carbonate solution, brine, dried over magnesium sulfate, and concentrated under vacuum. The crude residue was purified by silica gel

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chromatography (2:1 hexanes/ethyl acetate) and crystallization from ether and hexanes to yield 10 mg (19%) of white solid.  $R_f$  = 0.2 (2:1 hexanes/ethyl acetate);  $^1$ H-NMR ( $CDCl_3$ ):  $\delta$  7.69 (2H, d), 7.29-7.18 (6H, m), 6.96 (2H, d), 5.01-4.93 (1H, m), 4.93-4.85 (1H, m), 4.74-4.70 (1H, m), 4.51-4.45 (1H, m), 4.22-4.11 (1H, m), 3.95-3.72 (7H, m), 3.86 (3H, s), 3.00-2.80 (3H, m), 2.10-1.97 (2H, m), 1.79-1.67 (2H, m), 1.61-1.53 (2H, m), 1.38-1.02 (6H, m); MS (ESI):  $M+H=580$ .

10

Example 66

15

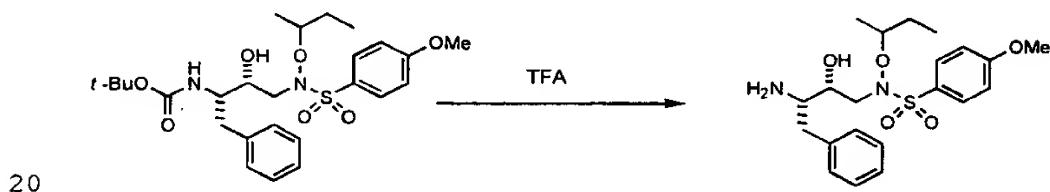
$(2S)-N^1-((1S,2R)-1\text{-benzyl-3-(cyclohexyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl}-2-[(2\text{-quinolinylcarbonyl)amino}]\text{butanediamide}$ . *tert*-butyl  $N$ -((1*S*,2*R*)-1-benzyl-3-(cyclohexyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate (0.18 mmol, 100 mg) was stirred in 1 mL trifluoroacetic acid (TFA) at room temperature for 1 hour. The TFA was removed under vacuum, and the resulting residue was dissolved in ethyl acetate, washed with 5% aq. potassium carbonate solution, brine, dried over magnesium sulfate, and concentrated to a residue. The resulting free amine,  $(2S)-4\text{-amino-4-oxo-2-[(2-quinolinylcarbonyl)amino] butanoic acid hydrochloride}$  (0.18 mmol, 56 mg), 1-hydroxybenzotriazole hydrate (0.18 mmol, 25 mg),  $N$ -(3-Dimethylaminopropyl)- $N'$ -ethylcarbodiimide hydrochloride (0.20 mmol, 38 mg), diisopropylethylamine

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(0.91 mmol, 0.157 mL) and anhydrous *N,N*-dimethylformamide (0.5 mL) were combined at room temperature and stirred for 15 hours. The crude reaction mixture was concentrated to a residue, dissolved in ethyl acetate, washed with 1N HCl, 5% aq. potassium carbonate solution, brine and dried over magnesium sulfate. The solution was concentrated to a residue, purified by silica gel chromatography (ethyl acetate), and lyophilized providing a fluffy white solid. H-1-NMR (CDCl<sub>3</sub>): δ 9.19-9.17 (1H, m), 8.32-8.30 (1H, m), 8.23-8.16 (2H, m), 7.89-7.87 (1H, m), 7.79-7.76 (3H, m), 7.65-7.61 (1H, m), 7.13-7.11 (2H, m), 7.05-6.94 (6H, m), 5.73-5.64 (1H, m), 5.41-5.33 (1H, m), 4.96-4.85 (1H, m), 4.28-4.08 (2H, m), 3.89-3.74 (1H, m), 3.86 (3H, s), 3.25 (1H, bs), 2.95-2.79 (5H, m), 2.65-2.60 (1H, m), 2.04 (2H, bs), 1.70 (2H, bs), 1.57-1.41 (1H, m), 1.30-1.10 (5H, m); MS (ESI): M+H=719.

Example 67

Step 1:

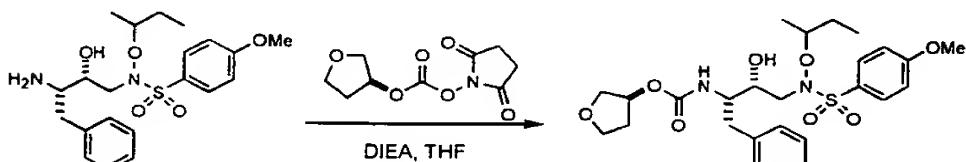


25 *N*-[(2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl]-*N*-(sec-butoxy)-4-methoxybenzene-sulfonamide. *tert*-butyl *N*-((1*S*,2*R*)-1-benzyl-3-sec-butoxy[(4-methoxyphenyl)sulfonyl]amino-2-hydroxy-propyl)carbamate (1.9 mmol, 1 g) was stirred in neat trifluoroacetic acid (TFA) at room temperature for 1 hour. The TFA was removed under vacuum, and the resulting residue was dissolved in ethyl acetate, washed with 5% aq. potassium carbonate solution, brine and dried over magnesium sulfate. 30 The dried solution was concentrated under vacuum and stored

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as a sticky white solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.81 (2H, d), 7.28-7.16 (5H, m), 7.01 (2H, d), 4.31 (2H, bs), 4.01-3.90 (1H, bs), 3.88 (3H, s), 3.5-2.5 (1H, bs), 3.33 (2H, bs), 2.89 (2H, bs), 2.63 (2H, bs), 1.71 (1H, bs), 1.43-1.40 (1H, m), 1.27-1.19 (3H, m), 0.98-0.85 (3H, m);  $\text{MS}$  (ESI):  $M+H=423$ .

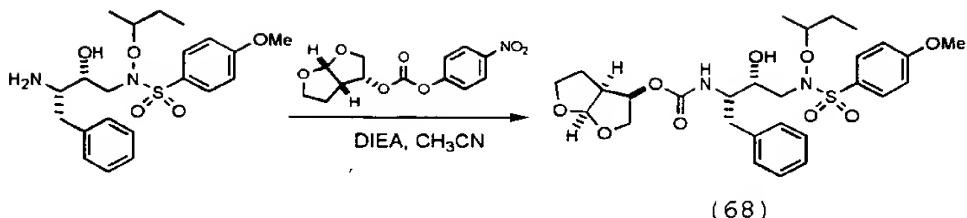
Step 2:



10

(67)

**(3S)-tetrahydro-3-furanyl N-((1S,2R)-1-benzyl-3-sec-butoxy[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate.**  $N$ -[(2R, 3S)-3-amino-2-hydroxy-4-phenylbutyl]- $N$ -(sec-butoxy)-4-methoxybenzenesulfon-amide (0.12 mmol, 50 mg), 1-((3S)-tetrahydro-3-furanyloxy)dihydro-1H-pyrrole-2,5-dione (0.12 mmol, 29 mg), diisopropylethylamine (0.18 mmol, 0.031 mL) and anhydrous THF (1 mL) were combined and stirred at room temperature for 20 hours. The reaction product was concentrated to a residue, purified directly by silica gel chromatography (2:1 hexanes/ethyl acetate) and crystallized from diethyl ether providing 40 mg (63%) of a white crystal.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.74-7.70 (2H, m), 7.30-7.17 (6H, m), 7.00-6.96 (2H, m), 5.11 (1H, bs), 4.75 (1H, bs), 4.31-4.30 (1H, m), 3.87 (3H, s), 3.87-3.75 (6H, m), 3.65-3.60 (1H, m), 3.21-2.64 (1H, bs), 2.89 (2H, bs), 2.15-2.01 (1H, m), 1.95-1.78 (1H, m), 1.78-1.58 (1H, m), 1.47-1.32 (1H, m), 1.24-1.13 (3H, m), 0.94-0.84 (3H, m);  $\text{MS}$  (ESI):  $M+Na=560$ .

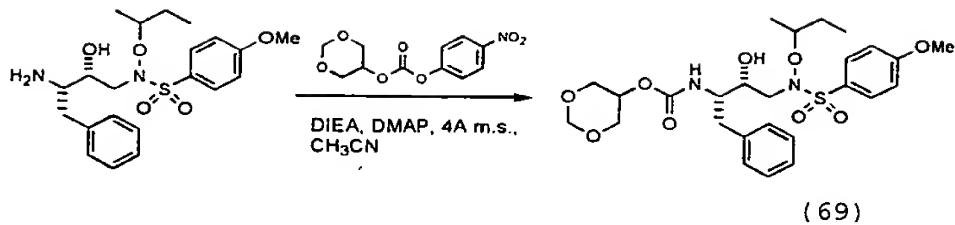
Example 68

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**(3R,3aS,6aR) hexahydrofuro[2,3-b]furan-3-yl N-((1S,2R)-1-benzyl-3-sec-butoxy[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate.** *N-[(2R,3S)-3-amino-2-hydroxy-4-phenylbutyl]-N-(sec-butoxy)-4-methoxybenzenesulfonamide*

10 (step 1, Example 67) (0.12 mmol, 50 mg) was combined with (2R,3aS,6aR) hexahydrofuro[2,3-b]furan-2-yl 4-nitrophenyl carbonate (0.12 mmol, 35 mg), diisopropylethylamine (0.18 mmol, 0.031 mL) and acetonitrile (1 mL). The reaction was allowed to stir at room temperature for 15 hours, then 15 heated to reflux for a minute and cooled to room temperature. The reaction was concentrated to a yellow oil, dissolved in ethyl acetate, washed with 1N HCl, saturated aq. sodium bicarbonate solution, brine and dried over magnesium sulfate. The crude product was purified by silica 20 gel chromatography (1:1 hexanes/ethyl acetate) and crystallization from an ether/hexanes solution to yield 30 mg (43%) of white crystals.  $R_f$  = 0.2 (1:1 hexanes/ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.74-7.71 (2H, m), 7.28-7.14 (6H, m), 7.00-6.97 (2H, m), 5.63-5.62 (1H, m), 5.05-4.93 (1H, m), 4.87-4.75 (1H, m), 4.36-4.23 (1H, m), 3.98-3.76 (4H, m), 3.87 (3H, s), 3.68 (2H, m), 3.10 (1H, bs), 3.08-2.70 (6H, m), 1.77-1.57 (1H, m), 1.50-1.32 (1H, m), 1.23-1.18 (3H, m), 0.93-0.86 (3H, m);  $\text{MS}$  (ESI):  $M+\text{Na}=601$ .

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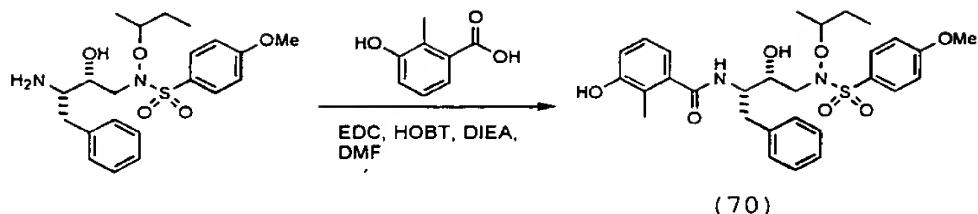
Example 69

5

1,3-dioxan-5-yl *N*-((1*S*,2*R*)-1-benzyl-3-sec-butoxy[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate. *N*-(2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*-(sec-butoxy)-4-methoxybenzenesulfon-amide (Step 1, Example 67) (0.09 mmol,

10 38 mg), 1,3-dioxan-5-yl 4-nitrophenyl carbonate (0.09 mmol, 24 mg), diisopropylethylamine (0.13 mmol, 0.024 mL), 4 Å molecular sieves, a crystal of *N,N*-dimethylaminopyridine and acetonitrile (1 mL) were combined and allowed to stir for 20 hours at room temperature. The reaction was then  
 15 concentrated to a residue, dissolved in ethyl acetate, washed with 1N HCl, 5% aq. potassium carbonate solution, brine, and dried over magnesium sulfate. The reaction was purified directly by crystallization from a solution of diethyl ether and hexanes to yield 30 mg (60%) of white  
 20 crystals. *R*<sub>f</sub> = 0.7 (1:1 hexanes/ethyl acetate); <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 7.72-7.69 (2H, m), 7.29-7.18 (6H, m), 6.98-6.95 (2H, m), 5.03-4.93 (1H, m), 4.93-4.87 (1H, m), 4.76-4.69 (1H, m), 4.53-4.44 (1H, m), 4.38-4.25 (1H, m), 3.95-3.72 (7H, m), 3.86 (3H, s), 3.24-2.62 (3H, m), 1.76-1.60 (1H, m),  
 25 1.47-1.29 (1H, m), 1.22-1.16 (3H, m), 0.94-0.83 (3H, m); MS (ESI): M+H=553.

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Example 70

5

*N- (sec-butoxy)-N- [(2R,3S)-2-hydroxy-3-(3-hydroxy-2-methoxybenzenesulfonyl)butyl]-4-methoxybenzenesulfonamide.*

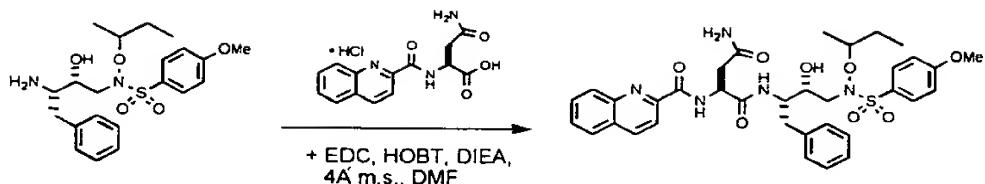
*N- [(2R,3S)-3-amino-2-hydroxy-4-phenylbutyl]-N- (sec-butoxy)-4-methoxybenzenesulfonamide* (Step 1, Example 67) (0.12 mmol,

10 50 mg), 3-hydroxy-2-methylbenzoic acid (0.12 mmol, 18 mg), 1-hydroxybenzotriazole hydrate (0.12 mmol, 16 mg), *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.13 mmol, 25 mg), diisopropylethylamine (0.14 mmol, 0.025 mL) and anhydrous *N,N*-dimethylformamide (0.5 mL) were

15 combined at room temperature and stirred for 18 hours. The crude reaction mixture was concentrated to a residue, dissolved in ethyl acetate, washed with 1N HCl, 5% aq. potassium carbonate solution, brine and dried over magnesium sulfate. The solution was concentrated to a residue,

20 purified by RPHPLC (water/acetonitrile) and lyophylized providing 20 mg (30%) of a white solid. *H*1-NMR (CDCl<sub>3</sub>):  $\delta$  7.76-7.73 (2H, m), 7.32-7.23 (5H, m), 7.00-6.97 (3H, m), 6.78-6.76 (1H, m), 6.56-6.53 (1H, m), 5.90 (1H, bs), 4.42-4.27 (2H, m), 4.09-3.95 (1H, m), 3.87 (3H, s), 3.25-2.27 (5H, m),

25 2.05-1.95 (3H, m), 1.77-1.58 (1H, m), 1.55-1.22 (1H, m), 1.24-1.20 (3H, m), 0.93-0.86 (3H, m); MS (ESI): M+H=557.

Example 71

(71)

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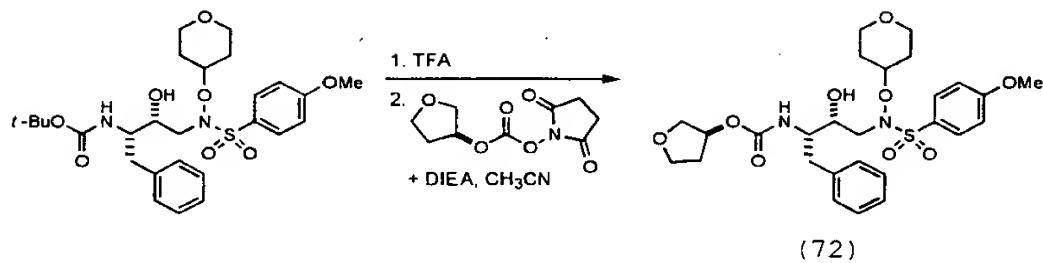
(2S)-N<sup>1</sup>-((1S,2R)-1-benzyl-3-sec-butoxy[4-methoxyphenyl]sulfonyl]amino-2-hydroxypropyl)-2-[(2-quinolinylcarbonyl)amino]butanediamide. N-[(2R,3S)-3-amino-2-hydroxy-4-phenylbutyl]-N-(sec-butoxy)-4-methoxybenzenesulfon-amide (Step 1, Example 67) (0.114 mmol, 48 mg), (2S)-4-amino-4-oxo-2-[(2-quinolinylcarbonyl)amino]butanoic acid hydrochloride (0.136 mmol, 42 mg), 1-hydroxybenzotriazole hydrate (0.136 mmol, 19 mg), N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.148 mmol, 28 mg), diisopropylethylamine (5.68 mmol, 0.990 mL) and anhydrous N,N-dimethylformamide (0.5 mL) were combined at room temperature and stirred for 15 hours. The crude reaction mixture was concentrated to a residue, dissolved in ethyl acetate, washed with 1N HCl, 5% aq. potassium carbonate solution, brine and dried over magnesium sulfate. The solution was concentrated to a residue, purified by silica gel chromatography (1:1 hexanes/ethyl acetate) and crystallization from ether and hexanes, providing 20 mg (25%) of a pink solid. H<sub>1</sub>-NMR (CDCl<sub>3</sub>): δ 9.20-9.18 (1H, m), 8.32-8.30 (1H, m), 8.22-8.16 (2H, m), 7.89-7.87 (1H, m), 7.80-7.76 (3H, m), 7.65-7.61 (1H, m), 7.14-7.11 (2H, m), 7.05-6.97 (6H, m), 5.76-5.64 (1H, bs), 5.49-5.26 (1H, m), 4.94-4.86 (1H, m), 4.36-4.14 (2H, m), 3.99-3.80 (1H, m), 3.86 (3H, s), 3.14 (1H, bs), 2.98-3.00 (5H, m), 2.71-2.59 (1H, m), 1.80-1.52 (1H, m), 1.48-1.30 (1H, m).

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(1H, m), 1.22-1.14 (3H, m), 0.94-0.80 (3H, m); MS (ESI):  
M+H=692.

Example 72

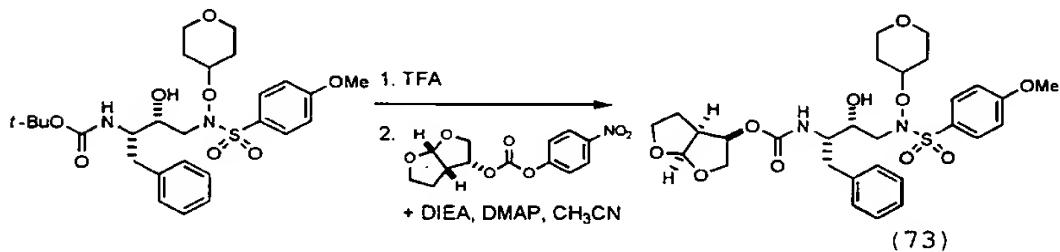
5



(3*S*) tetrahydro-3-furanyl *N*-(1*S*,2*R*)-1-benzyl-2-hydroxy-3-  
10 [[(4-methoxyphenyl)sulfonyl](tetrahydro-2*H*-pyran-4-  
yloxy)amino] propylcarbamate. *tert*-butyl *N*-(1*S*,2*R*)-1-  
15 benzyl-2-hydroxy-3-[(4-methoxyphenyl)sulfonyl](tetrahydro-  
2*H*-pyran-4-yloxy)amino]propylcarbamate, (Example 18), (0.09  
mmol, 50 mg) was stirred in 1 mL trifluoroacetic acid (TFA)  
15 at room temperature for 1 hour. The TFA was removed under  
vacuum, and the resulting residue was dissolved in ethyl  
acetate, washed with 1N HCl, 5% aq. potassium carbonate  
solution, brine, and dried over magnesium sulfate. The  
resulting free amine, 1-((3*S*)tetrahydro-3-  
20 furanyloxy)carbonyloxy)dihydro-1*H*-pyrrole-2,5-dione (0.09  
mmol, 22 mg), diisopropylethylamine (0.14 mmol, 0.024 mL)  
and acetonitrile (0.5 mL) were combined and stirred at room  
temperature for 30 minutes. The reaction product was  
concentrated to a residue, dissolved in ethyl acetate,  
25 washed with 1N HCl, 5% aq. potassium carbonate solution,  
brine, and dried over magnesium sulfate. The crude solution  
was concentrated, and the purified reaction product  
crystallized out of diethyl ether providing 28 mg (55%) of a  
white crystal.  $R_f$  = 0.1 (1:1 hexanes/ethyl acetate); H1-NMR

(CDCl<sub>3</sub>): δ 7.70 (2H, d), 7.32-7.15 (6H, m), 6.98 (2H, d), 5.11 (1H, bs), 4.81-4.71 (1H, m), 4.44-4.35 (1H, m), 3.97-3.70 (8H, m), 3.87 (3H, s), 3.65 (1H, m), 3.52-3.33 (2H, m), 3.25-2.5 (1H, bs), 2.93-2.88 (2H, m), 2.12-1.95 (3H, m), 1.93-1.80 (1H, m), 1.57-1.41 (2H, m); MS (ESI): M+H=565.

Example 73



10

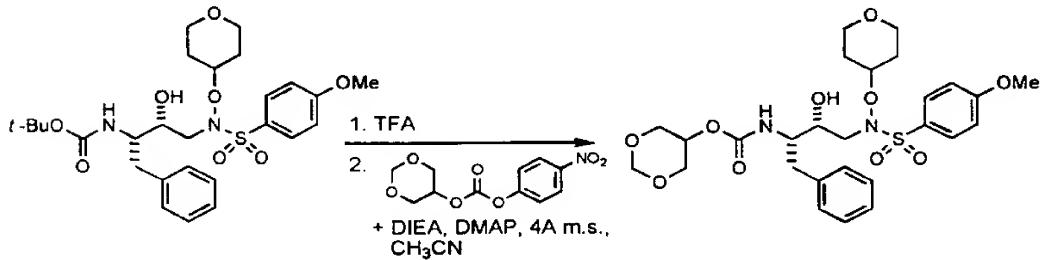
(3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-2-hydroxy-3-[(4-methoxyphenyl)sulfonyl](tetrahydro-2*H*-pyran-4-yloxy)amino]propylcarbamate

15     *tert*-butyl *N*-(1*S*,2*R*)-1-benzyl-2-hydroxy-3-[(4-methoxyphenyl)sulfonyl](tetrahydro-2*H*-pyran-4-yloxy)amino]propylcarbamate (Example 18), (0.09 mmol, 50 mg) was stirred in 1 mL trifluoroacetic acid (TFA) at room temperature for 1 hour. The TFA was removed under vacuum, and the resulting residue was dissolved in ethyl acetate, washed with 5% aq. potassium carbonate solution, brine, dried over magnesium sulfate, and concentrated to a residue. The resulting free amine, (2*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-2-yl 4-nitrophenyl carbonate (0.09 mmol, 27 mg), 20     diisopropylethylamine (0.14 mmol, 0.024 mL), a crystal of *N,N*-dimethylaminopyridine, 4 Å molecular sieves and acetonitrile (0.5 mL) were combined and stirred at room temperature for 15 hours. The reaction solution was concentrated to a residue, dissolved in ethyl acetate,

washed with 1N HCl, 5% aq. potassium carbonate solution, brine, dried over magnesium sulfate, and concentrated under vacuum. The crude residue was purified by silica gel chromatography (1:1 hexanes/ethyl acetate) and 5 crystallization from ether and hexanes to yield 20 mg (36%) of white crystals.  $R_f$  = 0.2 (1:1 hexanes/ethyl acetate);  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ):  $\delta$  7.71 (2H, d), 7.31-7.12 (6H, m), 6.99 (2H, d), 5.65-5.61 (1H, m), 5.05-4.95 (1H, m), 4.90-4.72 (1H, m), 4.49-4.34 (1H, m), 4.00-3.76 (7H, m), 3.88 (3H, s), 3.71-3.60 10 (2H, m), 3.48-3.35 (2H, m), 3.40-2.40 (1H, bs), 3.28-2.61 (5H, m), 3.04-2.71 (2H, m), 2.09-1.97 (2H, m); MS (ESI):  $M+\text{H} = 607$ .

Example 74

15



(74)

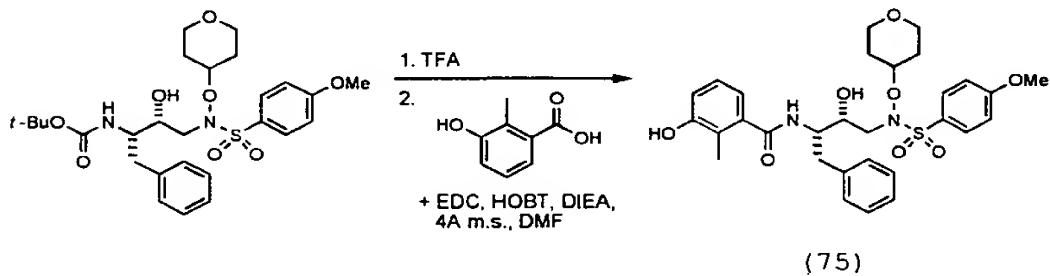
1,3-dioxan-5-yl *N*-(1*S*,2*R*)-1-benzyl-2-hydroxy-3-[(4-methoxyphenyl)sulfonyl](tetrahydro-2*H*-pyran-4-yloxy)amino]propylcarbamate. *tert*-butyl *N*-(1*S*,2*R*)-1-benzyl-2-hydroxy-3-[(4-methoxyphenyl)sulfonyl](tetrahydro-2*H*-pyran-4-yloxy)amino]propylcarbamate (Example 18), (0.09 20 mmol, 50 mg) was stirred in 1 mL trifluoroacetic acid (TFA) at room temperature for 5 hours. The TFA was removed under vacuum, and the resulting residue was dissolved in ethyl acetate, washed with 5% aq. potassium carbonate solution, brine, dried over magnesium sulfate, and concentrated to a 25

- 180 -

residue. The resulting free amine, 1,3-dioxan-5-yl 4-nitrophenyl carbonate (0.08 mmol, 22 mg), diisopropylethylamine (0.14 mmol, 0.024 mL), a crystal of *N,N*-dimethylaminopyridine, 4 Å molecular sieves and 5 acetonitrile (0.5 mL) were combined and stirred at room temperature for 20 hours. The reaction solution was concentrated to a residue, dissolved in ethyl acetate, washed with 1N HCl, 5% aq. potassium carbonate solution, brine, dried over magnesium sulfate, and concentrated under 10 vacuum. The crude residue was purified by silica gel chromatography (1:1 hexanes/ethyl acetate) and crystallization from ether and hexanes to yield 3 mg (6%) of white crystals.  $R_f$  = 0.2 (1:1 hexanes/ethyl acetate);  $\text{H}^1\text{-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.69 (2H, d), 7.32-7.17 (6H, m), 6.98 (2H, d), 15 5.02-4.94 (1H, m), 4.94-4.87 (1H, m), 4.76-4.69 (1H, m), 4.53-4.45 (1H, m), 4.45-4.34 (1H, m), 4.00-3.70 (9H, m), 3.87 (3H, s), 3.49-3.30 (2H, m), 3.10 (1H, bs), 3.47-3.35 (2H, m), 2.99-2.78 (2H, m), 2.07-1.95 (2H, m);  $\text{MS}$  (ESI):  $M+H=581$ .

20

Example 75



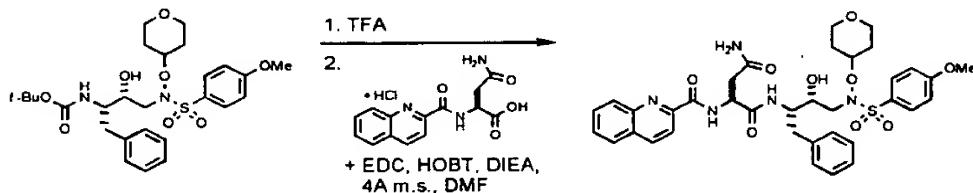
25 ***N*-(1*S*,2*R*)-1-benzyl-2-hydroxy-3-[(4-methoxyphenyl)sulfonyl](tetrahydro-2*H*-pyran-4-yloxy)amino]propyl-3-hydroxy-2-methylbenzamide.** *tert*-butyl *N*-(1*S*,2*R*)-1-benzyl-2-hydroxy-3-[(4-methoxyphenyl)sulfonyl](tetrahydro-2*H*-pyran-4-yloxy)amino]propylcarbamate (Example 18), (0.10 mmol, 54 mg)

- 181 -

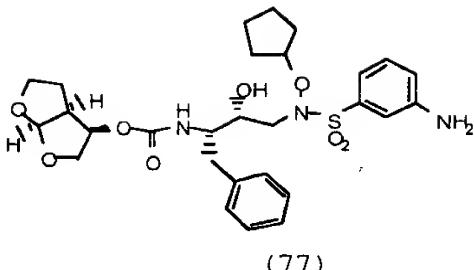
was stirred in 1 mL trifluoroacetic acid (TFA) at room temperature for 5 hours. The TFA was removed under vacuum, and the resulting residue was dissolved in ethyl acetate, washed with 5% aq. potassium carbonate solution, brine, 5 dried over magnesium sulfate, and concentrated to a residue. The resulting free amine, 3-hydroxy-2-methylbenzoic acid (0.10 mmol, 15 mg), 1-hydroxybenzotriazole hydrate (0.10 mmol, 14 mg), N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.11 mmol, 21 mg), diisopropylethylamine 10 (0.15 mmol, 0.026 mL) and anhydrous N,N-dimethylformamide (0.5 mL) were combined at room temperature and stirred for 20 hours. The crude reaction mixture was concentrated to a residue, dissolved in ethyl acetate, washed with 1N HCl, 5% aq. potassium carbonate solution, brine and dried over 15 magnesium sulfate. The solution was concentrated to a residue, and purified by crystallization from ether and hexanes providing 21 mg (37%) of a white solid.  $R_f = 0.2$  (1:1 hexanes/ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.73 (2H, d), 7.33-7.17 (5H, m), 7.02-6.94 (3H, m), 6.77 (1H, d), 6.53 (1H, d), 5.84-5.76 (1H, m), 4.49-4.28 (2H, m), 3.99-3.89 (3H, m), 3.87 (3H, s), 3.47-3.35 (2H, m), 3.50-2.50 (1H, bs), 20 3.14-3.04 (2H, m), 3.00-2.88 (2H, m), 2.08-1.88 (2H, m), 2.01 (3H, s), 1.7-1.3 (2H, m);  $\text{MS}$  (ESI):  $M+\text{H}=585$ .

25

Example 76

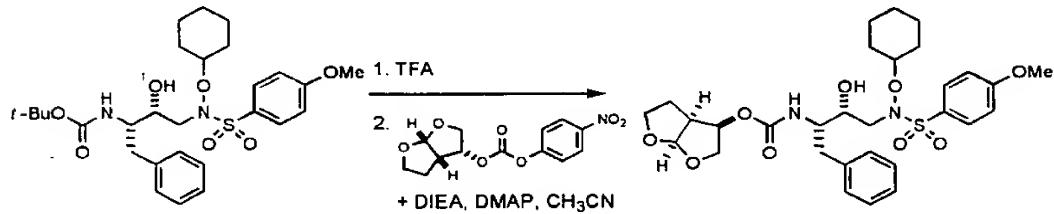


(2S)-N<sup>1</sup>-(1S,2R)-1-benzyl-2-hydroxy-3-[(4-methoxyphenyl)sulfonyl](tetrahydro-2H-pyran-4-yloxy)amino]propyl-2-[(2-quinolinylcarbonyl)amino]butanediamide. tert-butyl N-(1S,2R)-1-benzyl-2-hydroxy-3-[(4-methoxyphenyl)sulfonyl](tetrahydro-2H-pyran-4-yloxy)amino]propylcarbamate (Example 18), (0.09 mmol, 50 mg) was stirred in 1 mL trifluoroacetic acid (TFA) at room temperature for 5 hours. The TFA was removed under vacuum, and the resulting residue was dissolved in ethyl acetate, washed with 5% aq. potassium carbonate solution, brine, dried over magnesium sulfate, and concentrated to a residue. The resulting free amine, (2S)-4-amino-4-oxo-2-[(2-quinolinylcarbonyl)amino]butanoic acid hydrochloride (0.09 mmol, 28 mg), 1-hydroxybenzotriazole hydrate (0.09 mmol, 13 mg), N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.10 mmol, 19 mg), diisopropylethylamine (0.27 mmol, 0.047 mL) and anhydrous N,N-dimethylformamide (0.5 mL) were combined at room temperature and stirred for 20 hours. The crude reaction mixture was concentrated to a residue, dissolved in ethyl acetate, washed with 1N HCl, 5% aq. potassium carbonate solution, brine and dried over magnesium sulfate. The solution was concentrated to a residue, purified by silica gel chromatography (20:1 ethyl acetate/methanol) and crystallization from ether and hexanes, providing 6 mg (8%) of a pink solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ 9.18 (1H,d), 8.31 (1H,d), 8.24-8.13 (2H,m), 7.88 (1H,d), 7.80-7.74 (3H,m), 7.66-7.60 (1H,m), 7.15-7.08 (2H,m), 7.08-6.93 (6H,m), 5.74 (1H,bs), 5.46 (1H,bs), 4.94-4.85 (1H,m), 4.44-4.35 (1H,m), 4.27-4.18 (1H,m), 3.96-3.80 (3H,m), 3.88 (3H,s), 3.47-3.34 (2H,m), 3.14 (1H,bs), 2.98-2.76 (5H,m), 2.72-2.60 (1H,m), 2.09-1.95 (2H,bs), 1.65-1.39 (2H,m); MS (ESI): M+H=720.

Example 77

5

(3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(3-aminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate. This material was obtained from the corresponding m-nitro precursor (Example 100, Step 1) via 10 hydrogenation. The material was identical to isomer 1 of Example 31.

Example 78

15

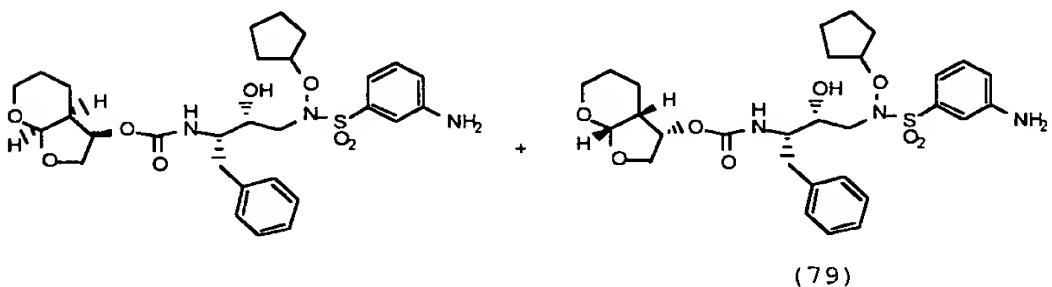
(3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-(cyclohexyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropylcarbamate. *tert*-butyl *N*-(1*S*,2*R*)-1-benzyl-3-(cyclohexyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropylcarbamate (0.09 mmol, 50 mg) was stirred in 1 mL trifluoroacetic acid (TFA) at room temperature for 5 hours. The TFA was removed under vacuum, and the resulting residue was dissolved in ethyl acetate, washed with 5% aq.

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potassium carbonate solution, brine, dried over magnesium sulfate, and concentrated to a residue. The resulting free amine, (2*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-2-yl 4-nitrophenyl carbonate (0.09 mmol, 27 mg),

5 diisopropylethylamine (0.13 mmol, 0.018 mL), a crystal of *N,N*-dimethylaminopyridine, 4 Å molecular sieves and acetonitrile (0.5 mL) were combined and stirred at room temperature for 3 days. The reaction solution was concentrated to a residue, dissolved in ethyl acetate, 10 washed with 1N HCl, 5% aq. potassium carbonate solution, brine, dried over magnesium sulfate, and concentrated under vacuum. The crude residue was purified by crystallization from ether to yield 15 mg (27%) of white crystals.  $^1$ H-NMR ( $\text{CDCl}_3$ ):  $\delta$  7.71 (2H, d), 7.28-7.16 (6H, m), 6.97 (2H, d), 5.63-5.61 (1H, m), 5.00-4.98 (1H, m), 4.87-4.77 (1H, m), 4.24- 15 4.11 (1H, m), 3.98-3.79 (4H, m), 3.87 (3H, s), 3.72-3.61 (2H, m), 3.05 (1H, bs), 3.05-2.72 (6H, m), 2.10-1.98 (2H, m), 1.78-1.68 (2H, m), 1.37-1.04 (6H, m); MS (ESI):  $M+H=605$ .

20

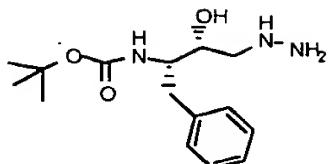
Example 79

25 (3*S*,3*aR*,7*aS*)hexahydro-4*H*-furo[2,3-*b*]pyran-3-yl *N*-(1*S*,2*R*)-3-[(3-aminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate + (3*R*,3*aS*,7*aR*)hexahydro-4*H*-furo[2,3-*b*]pyran-3-yl *N*-(1*S*,2*R*)-3-[(3-aminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-

**hydroxypropylcarbamate.** A mixture of (3*R*, 3*aS*, 7*aR*) + (3*S*, 3*aR*, 7*aS*) hexahydro-4*H*-furo[2, 3-*b*]pyran-3-yl (4-nitrophenyl) carbonate (332 mg, 1.074 mmol, WO 9633187), 3-amino-*N*<sup>1</sup>-[(2*R*, 3*S*)-3-amino-2-hydroxy-4-phenylbutyl]-*N*<sup>1</sup>- (cyclopentyloxy)-1-benzenesulfonamide (Step 1, Example 27), (150 mg, 0.358 mmol) and N,N-diisopropylethylamine (249  $\mu$ L, 1.432 mmol) were combined in approximately 3 mL of acetonitrile and stirred at ambient temperature under an Argon atmosphere for 18 hours. The reaction solvent was removed *in vacuo* and the residue was partitioned between dichloromethane and 1N NaOH. After separating the layers, the aqueous phase was extracted with dichloromethane. The combined organic layers were combined, dried over anhydrous magnesium sulfated, filtered and evaporated *in vacuo*. The residue was purified on three preparative silica gel TLC plates (20x20 cm, 1000  $\mu$ M) eluting with 65:35 ethyl acetate : hexane. The product band was removed, eluted with 4:1 methylene chloride : methanol, filtered, and evaporated *in vacuo*. The residue was dissolved in dichloromethane, dried over anhydrous magnesium sulfate, filtered, evaporated *in vacuo*, and dried under high vacuum to provide a 1:1 mixture of (3*S*, 3*aR*, 7*aS*) hexahydro-4*H*-furo[2, 3-*b*]pyran-3-yl *N*-(1*S*, 2*R*)-3-[(3-aminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate and (3*R*, 3*aS*, 7*aR*) hexahydro-4*H*-furo[2, 3-*b*]pyran-3-yl *N*-(1*S*, 2*R*)-3-[(3-aminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate (146 mg, 69%) as a foam.  $^1$ H-NMR (methanol-D<sub>4</sub>) 1.14 (m, 1H), 1.78 (m, 11H), 2.56 (m, 1H), 3.05 (m, 3H), 3.41 (m, 1H), 3.76 (m, 5H), 4.06 (m, 1H), 4.84 (m, 1H), 4.96 (m, 1H), 5.06 (m, 1H), 6.93 (m, 1H), 7.02 (m, 1H), 7.09 (m, 1H), 7.14 (m, 1H), 7.22 (m, 5H). MS(ESI): 612 (M+Na).

Example 80

Step 1:

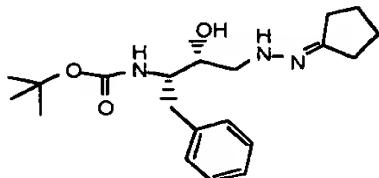


5

**tert-butyl N-[(1S,2R)-1-benzyl-3-hydrazino-2-hydroxypropyl]carbamate.** A mixture of tert-butyl N-(1S)-1-[(2S)oxiran-2-yl]-2-phenylethylcarbamate (2.50 g, 9.51 mmol) and anhydrous hydrazine (3.00 mL, 95.0 mmol) in 15 mL of

10 isopropanol was heated at reflux under an Argon atmosphere for 18 hours. The reaction solvent was removed in *vacuo* and the residue was triturated with diethylether, filtered and dried under high vacuum to provide tert-butyl N-[(1S,2R)-1-benzyl-3-hydrazino-2-hydroxypropyl]carbamate (1.766 g, 63%) as a white solid.  $^1\text{H-NMR}$  (chloroform-D3) 1.35 (d, 9H), 1.67 (b, 4H), 2.89 (m, 4H), 3.91 (m, 3H), 4.63 (m, 1H), 7.25 (m, 5H). MS (ESI): 318 (M+Na).

Step 2:



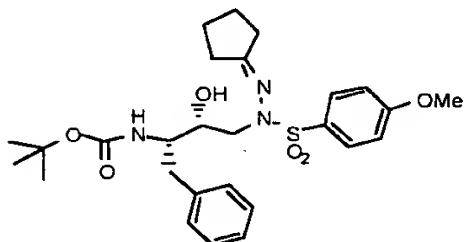
20

**tert-butyl N-[(1S,2R)-1-benzyl-3-(2-cyclopentylidenhydrazino)-2-hydroxypropyl]carbamate.**

25 A solution of tert-butyl N-[(1S,2R)-1-benzyl-3-hydrazino-2-hydroxypropyl]carbamate (500 mg, 1.695 mmol) in 5 mL of isopropanol under Argon was treated with cyclopentanone (180

μL, 2.034 mmol). After stirring for approximately 18 hours, the reaction solvent was removed *in vacuo* and the residue was triturated with diethylether. The slurry was filtered and the solid was dried under high vacuum to provide *tert*-  
5 butyl *N*-[(1*S*,2*R*)-1-benzyl-3-(2-cyclopentylidenhydrazino)-2-  
hydroxypropyl]carbamate (85 mg, 14%) as a white solid. *H*1-  
NMR (chloroform-D3) 1.34 (s, 9H), 1.54 (b, 2H), 1.73 (m,  
2H), 1.83 (m, 2H), 2.22 (m, 2H), 2.35 (m, 2H), 2.90 (m, 1H),  
3.02 (m, 1H), 3.14 (m, 1H), 3.38 (m, 1H), 3.64 (bm, 1H),  
10 3.84 (bm, 1H), 4.52 (m, 1H), 7.25 (m, 5H). MS (APCI):  
361 (M+Na).

## Step 3:



15

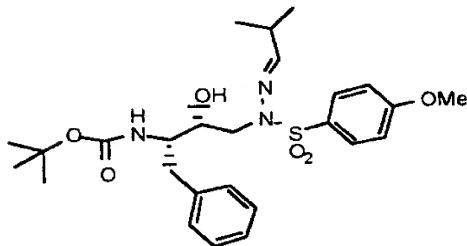
(80)

*tert*-butyl *N*-[(1*S*,2*R*)-1-benzyl-3-(2-cyclopentyliden-1-[(4-methoxyphenyl)sulfonyl]hydrazino-2-hydroxypropyl)carbamate. A solution of *tert*-butyl *N*-[(1*S*,2*R*)-1-benzyl-3-(2-cyclopentylidenhydrazino)-2-hydroxypropyl]carbamate (76 mg, 0.210 mmol) in 2 mL of dichloromethane at ambient 20 temperature under Argon was treated with 4-methoxyphenylsulphonylchloride (46 mg, 0.221 mmol) and *N,N*-diisopropylethylamine (38.5 μL, 0.221 mmol) and allowed to 25 stir at ambient temperature over approximately 18 hours. The reaction solvent was removed *in vacuo* and the residue was purified on flash grade silica gel eluting with 2:3 ethyl acetate : hexane. Fractions containing the product

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were combined, evaporated *in vacuo* to a residue and triturated with hexane and diethyl ether. The solvents were removed *in vacuo* and the residual solid was dried under high vacuum to provide *tert*-butyl *N*-((1*S*,2*R*)-1-benzyl-3-2-5 cyclopentyliden-1-[(4-methoxyphenyl)sulfonyl]hydrazino-2-hydroxypropyl)carbamate (26 mg, 23%) as a solid. <sup>1</sup>H-NMR (chloroform-D3): 1.34 (m, 9H), 1.62 (m, 4H), 1.83 (m, 2H), 2.42 (m, 1H), 2.87 (m, 3H), 3.12 (m, 1H), 3.58 (m, 1H), 3.83 (m, 5H), 4.32 (m, 1H), 4.57 (b, 1H), 6.97 (m, 2H), 7.20 (m, 10 5H), 7.69 (m, 2H). MS (APCI): 554 (M+Na).

Example 81

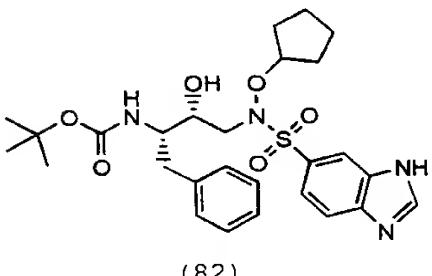


15 (81)

15 *tert*-butyl *N*-((1*S*,2*R*)-1-benzyl-2-hydroxy-3-1-[(4-methoxyphenyl)sulfonyl]-2-[(*Z*)-2-methylpropylidene]hydrazinopropyl)carbamate. A solution of *tert*-butyl *N*-[(1*S*,2*R*)-1-benzyl-3-hydrazino-2-hydroxypropyl]carbamate (Step 1, Example 80), (100 mg, 0.339 mmol) in approximately 2 mL of dichloromethane under Argon was treated with isobutyraldehyde (46.2  $\mu$ L, 0.508 mmol). After stirring at ambient temperature for 20 minutes, 4-methoxyphenylsulphonylchloride (77 mg, 0.372 mmol) and *N,N*-diisopropylethylamine (88.6  $\mu$ L, 0.508 mmol) were added and the reaction was maintained for an additional 18 hours. The reaction mixture was evaporated *in vacuo* and purified on

flash grade silica gel eluting with 3:7 ethyl acetate : hexane. Fractions containing the product were combined, evaporated *in vacuo*, and crystallized from ethyl acetate and hexane. The slurry was filtered, washed with hexane, and 5 dried under high vacuum to provide *tert*-butyl *N*-(*(1S,2R)*-1-benzyl-2-hydroxy-3-[(4-methoxyphenyl)sulfonyl]-2-[*(Z*)-2-methylpropylidene] hydrazinopropyl)carbamate (34 mg, 19 %) as a solid. *H*-NMR (chloroform-D3): 1.00 (m, 6H), 1.44 (s, 9H), 1.77 (m, 1H), 2.57 (m, 1H), 2.94 (m, 3H), 3.54 (m, 1H), 10 3.93 (s, 3H), 3.94 (m, 2H), 4.35 (m, 1H), 7.02 (m, 2H), 7.17 (m, 2H), 7.31 (m, 4H), 7.81 (m, 2H). MS(ESI): 542 (M+Na).

Example 82



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(82)

*tert*-butyl *N*-(*1S,2R*)-3-[(1*H*-benzimidazol-6-ylsulfonyl) (cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate. A solution of *tert*-butyl *N*-(*(1S,2R)*-1-benzyl-3-(cyclopentyloxy) [(3,4-diaminophenyl)sulfonyl]amino-2-hydroxypropyl)carbamate (Step 4, Example 10), (0.600 g, 1.12 mmol) in absolute ethanol (15 mL) was treated 20 with triethylorthoformate (280  $\mu$ L, 1.69 mmol) followed by trifluoroacetic acid (15  $\mu$ L, 0.19 mmol). After stirring at ambient temperature under an Argon atmosphere for 1.5 hrs., the reaction mixture was quenched with several drops of 5% w/v aqueous potassium carbonate and evaporated *in vacuo*. The residue was purified on flash grade silica gel 25

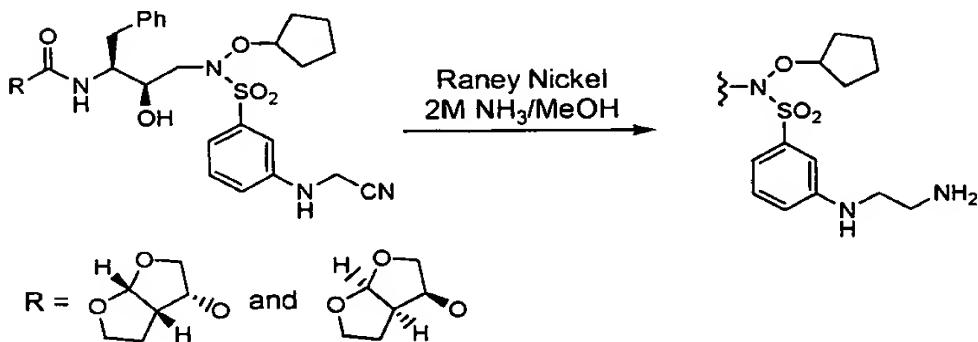
sequentially eluting with 4:1 ethyl acetate : hexane (0.5 L); ethyl acetate (0.5 L); and 95:5 ethyl acetate : methanol (0.5 L). Fractions containing the product were combined, evaporated *in vacuo* to a residue and dried under high vacuum

5 to provide *tert*-butyl *N*-(1*S*,2*R*)-3-[(1*H*-benzimidazol-6-ylsulfonyl)(cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate (0.570 g, 93%).  $^1\text{H-NMR}$  (dimethylsulfoxide-D6): 1.14 (s, 9H), 1.72 (m, 8H), 2.47 (m, 1H), 2.70 (m, 1H), 2.99 (m, 2H), 3.55 (m, 2H), 4.85 (m, 1H), 5.14 (m, 1H), 6.67 (d, 1H), 7.20 (m, 6H), 7.61 (d, 1H), 7.81 (d, 1H), 8.04 (s, 1H), 8.52 (s, 1H).  $\text{MS}(\text{ESI})$ :

10 545 ( $\text{M}+\text{H}$ ).

Example 83

15



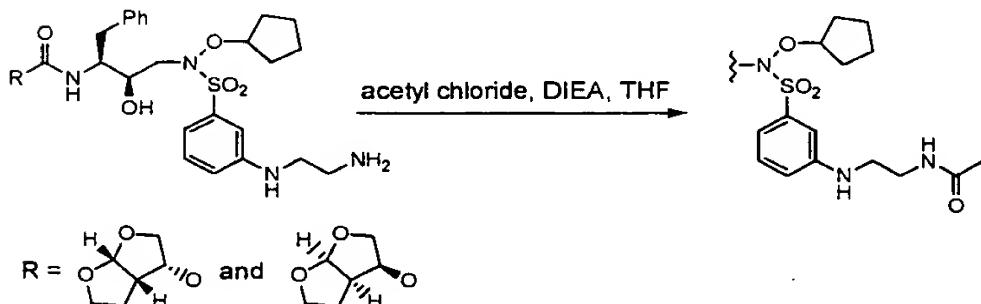
(3*R*,3*aS*,6*aR*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(3-20 [(2-aminoethyl)amino]phenylsulfonyl)(cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate and (3*S*,3*aR*,6*aS*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(3-[(2-aminoethyl)amino]phenylsulfonyl)(cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate. A solution of 25 mg

25 (0.041 mmol) of a 1:1 mixture of

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(3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-[(3-[(cyanomethyl)amino]phenylsulfonyl)(cyclopentyloxy)amino]-2-hydroxypropylcarbamate and (3*S*,3a*R*,6a*S*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-[(3-[(cyanomethyl)amino]phenylsulfonyl)(cyclopentyloxy)amino]-2-hydroxypropylcarbamate (see example 86) in 8 mL of 2M NH<sub>3</sub>/MeOH in a Parr bottle was treated with approximately 20 mg of Raney nickel. The resulting mixture was subjected to hydrogenation at 30 psi for 1 hour. The vessel was purged, catalyst removed by filtration through celite and the filtrate concentrated *in vacuo*. The residue was dissolved in a minimum volume of CH<sub>2</sub>Cl<sub>2</sub> and the solution added dropwise to rapidly stirred 1:1 ether/hexane. A white solid precipitated which was collected by filtration and dried *in vacuo*. yield=16 mg (64%). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 7.32-7.03 (7H), 6.95-6.78 (3H), 6.20 (1H), 5.45 (1H), 5.19 (1H), 4.82-4.65 (2H), 3.81-3.40 (7H), 3.18-2.60 (9H), 2.39 (1H), 1.93-1.04 (10H). MS (ESI): 619 (M+H).

20

Example 84

(84)

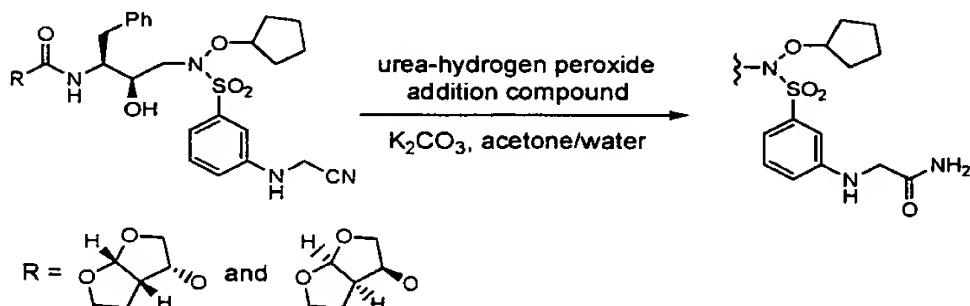
25 (3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(3-[2-(acetylamino)ethyl]aminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate and

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(3*S*,3a*R*,6a*S*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(3-[2-(acetylamino)ethyl]aminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate. A solution of 33 mg (0.053 mmol) of a 1:1 mixture of

5 (3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(3-[2-aminoethyl]amino)phenylsulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate and (3*S*,3a*R*,6a*S*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(3-[2-aminoethyl]amino)phenylsulfonyl](cyclopentyloxy)amino]-10 1-benzyl-2-hydroxypropylcarbamate in 3 mL of anhydrous THF at 0°C was treated with 0.010 mL (0.058 mmol) of *N,N*-diisopropylethylamine followed by 0.004 mL (0.06 mmol) of acetyl chloride. The resulting solution was allowed to warm to RT with stirring. After 18 hours the solution was 15 concentrated *in vacuo* and the residue subjected to flash chromatography (silica gel, 95:5 CH<sub>2</sub>Cl<sub>2</sub>/2M NH<sub>3</sub> in MeOH) to afford 30 mg (86%) of the desired product as a white foam. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.71-7.00 (10H), 6.90 (1H), 6.40-6.02 (1H), 5.62 (1H), 5.32 (1H), 4.99 (1H), 4.80 (1H), 4.02-3.40 (7H), 20 3.38-2.60 (8H), 2.20-1.40 (13H). LCMS (ESI): 661 (M+H).

Example 85



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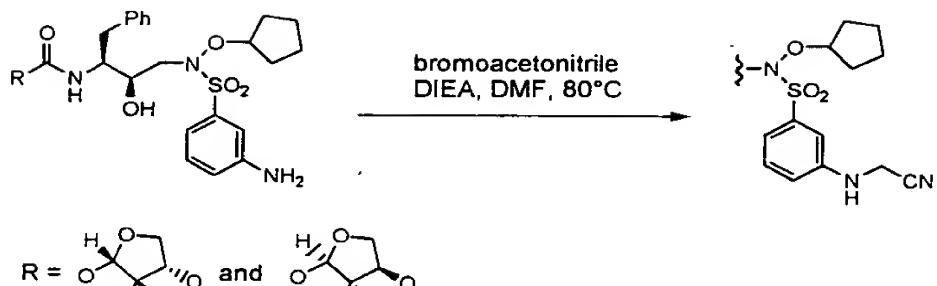
(3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(3-  
[(2-amino-2-oxoethyl)amino]phenylsulfonyl)  
(cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate and  
(3*S*,3a*R*,6a*S*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(3-  
5 [(2-amino-2-oxoethyl)amino]phenylsulfonyl)  
(cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate.

A solution of 0.100 g (0.163 mmol) of a 1:1 mixture of  
(3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-  
benzyl-3-[(3-[(cyanomethyl)amino]phenylsulfonyl)  
10 (cyclopentyloxy)amino]-2-hydroxypropylcarbamate and  
(3*S*,3a*R*,6a*S*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-  
benzyl-3-[(3-[(cyanomethyl)amino]phenylsulfonyl)  
(cyclopentyloxy)amino]-2-hydroxypropylcarbamate (see example  
86) and 5.0 mg (0.033 mmol) of K<sub>2</sub>CO<sub>3</sub> in 2 mL of 3:1

15 acetone/water was treated with 0.150 g (1.63 mmol) of urea-  
hydrogen peroxide addition compound and stirred at RT.

After 18 hours tlc (silica gel, 95:5 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) indicated  
no remaining starting material at R<sub>f</sub>=0.43, a major new  
component at R<sub>f</sub>=0.21, and a lesser component at R<sub>f</sub>=0.61.

20 The solution was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with water  
(3x), dried over anhydrous MgSO<sub>4</sub>, and concentrated. The  
residue was subjected to flash chromatography (silica gel,  
95:5 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to afford 49 mg (46%) of the R<sub>f</sub>=0.21  
product as a white foam. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.46-6.92 (11H),  
25 6.60-5.80 (2H), 5.60 (2H), 5.06-4.77 (2H), 4.03-3.40 (7H),  
3.24-2.43 (6H), 1.91-1.32 (10H). LCMS (ESI): 633 (M+H).

Example 86

5

(3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-

benzyl-3-[(3-[(cyanomethyl)amino]phenylsulfonyl)

(cyclopentyloxy)amino]-2-hydroxypropylcarbamate and

(3*S*,3a*R*,6a*S*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-

10 benzyl-3-[(3-[(cyanomethyl)amino]phenylsulfonyl)(cyclo-  
pentyloxy)amino]-2-hydroxypropylcarbamate

A solution of 0.200 g (0.347 mmol) of a 1:1 mixture of

(3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-

benzyl-3-(cyclopentyloxy)[(3-aminophenyl)sulfonyl]amino-2-

15 hydroxypropylcarbamate and (3*S*,3a*R*,6a*S*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(3-  
aminophenyl)sulfonyl]amino-2-hydroxypropylcarbamate (see

example 31), 0.050 mL (0.70 mmol) of bromoacetonitrile, and

0.12 mL (0.70 mmol) of *N,N*-diisopropylethylamine in 5 mL of

20 anhydrous DMF was heated to 80°C with stirring in a sealed  
tube. After 21 hours the solution was cooled to RT and

concentrated *in vacuo*. The residue was dissolve in CH<sub>2</sub>Cl<sub>2</sub>.

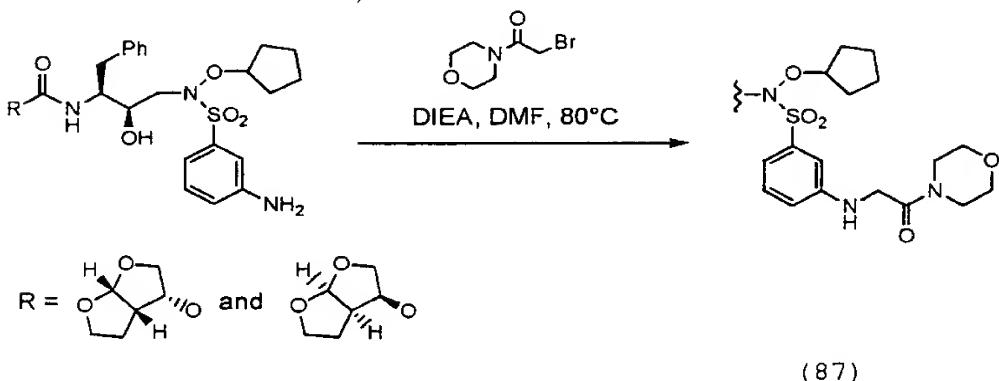
The resulting solution was washed with aqueous brine (3x),  
dried over anhydrous MgSO<sub>4</sub>, and concentrated to dryness.

25 The crude product was purified by flash chromatography  
(silica gel, 95:5 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to afford 145 mg (67%) of the  
desired product as a tan solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 7.41

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(1H), 7.28-6.99 (9H), 6.83 (1H), 5.46 (1H), 5.20 (1H), 4.82-4.63 (2H), 4.30 (2H), 3.80-3.40 (5H), 3.04-2.60 (5H), 2.40 (1H), 1.98-1.10 (10H). MS (ESI): 615 (M+H).

5

Example 87

10 (3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-[ (cyclopentyloxy) (3-[(2-morpholino-2-oxoethyl)amino]phenylsulfonyl)amino]-2-hydroxypropylcarbamate and (3*S*,3a*R*,6a*S*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-[ (cyclopentyloxy) (3-[(2-morpholino-2-oxoethyl)amino]phenylsulfonyl)amino]-2-hydroxypropylcarbamate. A solution of 0.100 g (0.174 mmol) of a 1:1 mixture of (3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy) [(3-aminophenyl)sulfonyl]amino-2-hydroxypropylcarbamate and

15 (3*S*,3a*R*,6a*S*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy) [(3-aminophenyl)sulfonyl]amino-2-hydroxypropylcarbamate (see example 31), 54.0 mg (0.261 mmol) of *N*-(bromoacetyl)morpholine, and 0.050 mL (0.26 mmol) of *N,N*-diisopropylethylamine in 4 mL of anhydrous DMF was

20 heated to 80°C with stirring in a sealed tube. After 4.5 hours the solution was cooled to RT and was treated with an

25

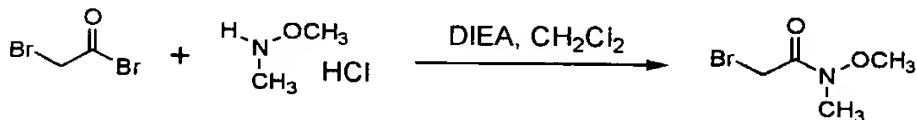
- 196 -

additional 54.0 mg of *N*-(bromoacetyl)morpholine, and 0.050 mL (0.26 mmol) of *N,N*-diisopropylethylamine. The solution was heated at 80°C for an additional 18 hours, cooled to RT, and concentrated *in vacuo*. The crude product was purified 5 by flash chromatography (silica gel, EtOAc) to give a viscous yellow oil. This material was dissolved in a minimum volume of CH<sub>2</sub>Cl<sub>2</sub> and the solution was added to rapidly stirred 1:1 ether/hexane. A white solid precipitated which was collected by filtration and dried *in* 10 *vacuo*. yield=54 mg (44%). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 7.31-7.06 (7H), 7.03-6.83 (3H), 6.26 (1H), 5.45 (1H), 5.18 (1H), 4.71 (2H), 3.92 (2H), 3.79-3.22 (13H), 3.08-2.60 (5H), 2.39 (1H), 1.95-1.04 (10H). LCMS (ESI): 703 (M+H).

15

Example 88

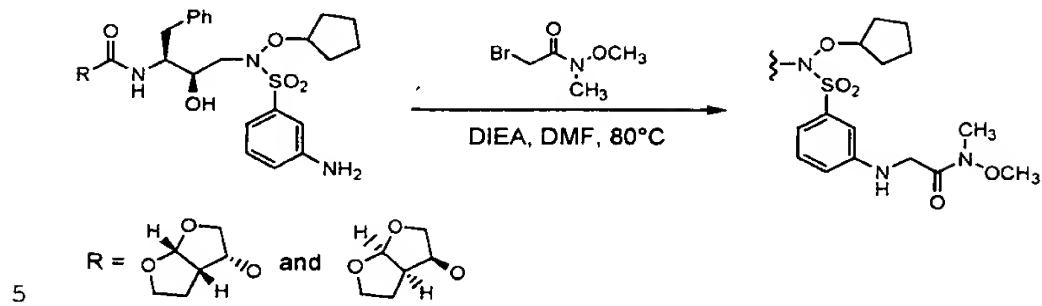
step 1:

20 **N-methoxy-N-methylbromoacetamide**

A solution of 4.5 mL (51.3 mmol) of bromoacetyl bromide and 5.00 g (51.3 mmol) of *N,O*-dimethylhydroxylamine hydrochloride in 80 mL of anhydrous CH<sub>2</sub>Cl<sub>2</sub> at 0°C was treated with a solution of 18.7 mL (108 mmol) of *N,N*-25 diisopropylethylamine in 40 mL of CH<sub>2</sub>Cl<sub>2</sub> via addition funnel over 10 minutes. A dark brown solution resulted which was allowed to warm to RT. After 18 hours the solution was washed with 5% aqueous citric acid (3x), saturated aqueous NaHCO<sub>3</sub> (3x), dried over MgSO<sub>4</sub>, and concentrated to give a 30 dark brown oil. This material was subjected to flash chromatography (8:2 to 6:4 hexane/EtOAc) to afford 2.97 g

(32%) of the desired product as a yellow-brown liquid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 4.22 (2H), 3.72 (3H), 3.20 (3H).

step 2:



(3*R*,3*aS*,6*aR*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-benzyl-3-((cyclopentyloxy)[3-(2-[methoxy(methyl)amino]-2-

10 oxoethylamino)phenyl]sulfonylamino)-2-

hydroxypropyl]carbamate and (3*S*,3*aR*,6*aS*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-benzyl-3-((cyclopentyloxy)[3-(2-[methoxy(methyl)amino]-2-

oxoethylamino)phenyl]sulfonylamino)-2-

15 hydroxypropyl]carbamate. A solution of 0.100 g (0.174 mmol) of a 1:1 mixture of (3*R*,3*aS*,6*aR*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(3-aminophenyl)sulfonyl]amino-2-hydroxypropyl)carbamate and (3*S*,3*aR*,6*aS*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(3-aminophenyl)sulfonyl]amino-2-hydroxypropyl)carbamate (see example 31), 40.0 mg (0.210 mmol) of *N*-methoxy-*N*-methylbromoacetamide, and 0.040 mL (0.21 mmol) of *N,N*-diisopropylethylamine in 3 mL of anhydrous DMF was heated to 80°C with stirring in a sealed tube. After 24 hours the solution was cooled to RT and was treated with an additional 20.0 mg of *N*-methoxy-*N*-methylbromoacetamide and 0.020 mL of *N,N*-

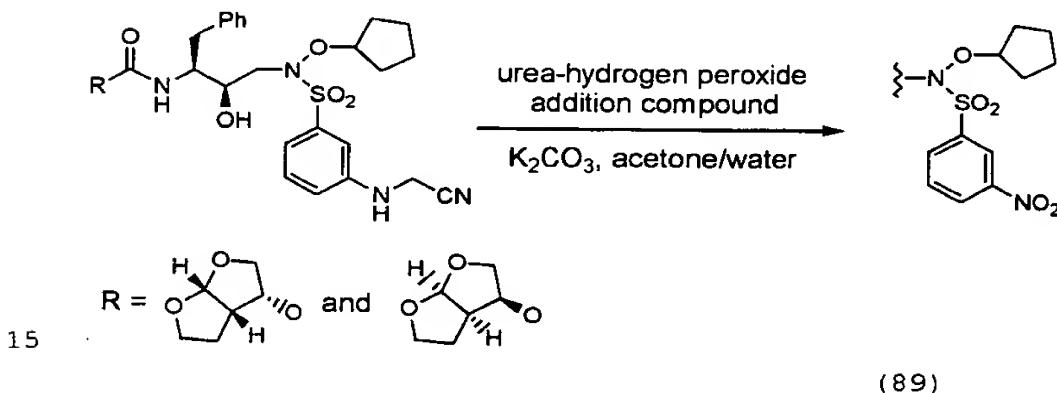
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diisopropylethylamine. The solution was again warmed to 80°C. After an additional 18 hours the solution was cooled to RT and was concentrated *in vacuo*. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub>. The solution was washed with saturated aqueous brine (3x), dried over MgSO<sub>4</sub>, and concentrated to dryness. The crude product was purified by flash chromatography (silica gel, 85:15 hexane/EtOAc) to afford 40 mg (34%) of the desired product as a white foam. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.40-6.84 (11H), 5.62 (1H), 5.18-4.87 (2H), 4.81 (1H), 4.05 (2H), 3.99-3.53 (8H), 3.26-2.70 (9H), 1.92-1.41 (10H). LCMS (ESI): 677 (M+H).

Example 89



(3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(3-nitrophenyl)sulfonyl]amino-2-hydroxypropyl)carbamate and (3*S*,3a*R*,6a*S*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(3-nitrophenyl)sulfonyl]amino-2-hydroxypropyl)carbamate

A solution of 0.100 g (0.163 mmol) of a 1:1 mixture of (3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-[(3-(cyanomethyl)amino)phenylsulfonyl](cyclopentyloxy)amino]-2-hydroxypropylcarbamate and

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(3*S*,3a*R*,6a*S*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-[ (3-[ (cyanomethyl)amino]phenylsulfonyl) (cyclopentyloxy)amino]-2-hydroxypropylcarbamate (see example 86) and 5.0 mg (0.033 mmol) of K<sub>2</sub>CO<sub>3</sub> in 2 mL of 3:1

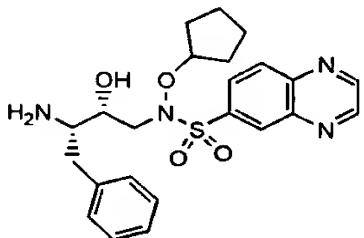
5 acetone/water was treated with 0.150 g (1.63 mmol) of urea-hydrogen peroxide addition compound and was stirred at RT. After 18 hours tlc (silica gel, 95:5 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) indicated no remaining starting material at R<sub>f</sub>=0.43, a major new component at R<sub>f</sub>=0.21, and a lesser component at R<sub>f</sub>=0.61.

10 The solution was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with water (3x), dried over anhydrous MgSO<sub>4</sub>, and concentrated. The residue was subjected to flash chromatography (silica gel, 95:5 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to afford 15 mg (15%) of the R<sub>f</sub>=0.61 product as a white foam. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 8.62 (1H), 8.51 (1H), 8.06 (1H), 7.75 (1H), 7.31-7.14 (6H), 5.65 (1H), 5.08-4.78 (3H), 3.98-3.57 (5H), 3.22-2.60 (6H), 1.95-1.40 (10H). LCMS (ESI): 606 (M+H).

15

Example 90

20 Step 1



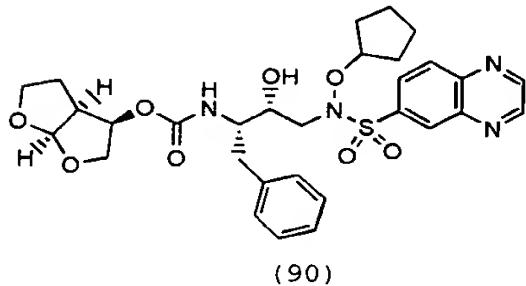
(3*R*,4*S*)-4-amino-1-(cyclopentyloxy)-5-phenyl-1-(6-quinoxalinylsulfonyl)-3-pentanol.

25 A mixture of *tert*-butyl *N*[(1*S*,2*R*)-1-benzyl-4-(cyclopentyloxy)-2-hydroxy-4-(6-quinoxalinylsulfonyl)butyl]carbamate (563 mg, 1.01 mmol) and trifluoroacetic acid (5 mL) was stirred under an Argon atmosphere for 0.5 hrs. The acid was removed in vacuo and

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the residue was partitioned between dichloromethane and 1N sodium hydroxide. The organic layer was separated and the aqueous layer was extracted again with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate, filtered and evaporated in vacuo. The crude product was purified on flash grade silica gel eluting with dichloromethane : méthanol (98:2). Fractions containing the product were combined and evaporated in vacuo and dried under high vacuum to provide (3*R*,4*S*)-4-amino-1-  
 5 (cyclopentyloxy)-5-phenyl-1-(6-quinoxalinylsulfonyl)-3-pentanol as a foam (379 mg, 82 %).  $^1\text{H-NMR}$  (chloroform-D3):  
 10 1.66 (m, 1H), 2.51 (m, 1H), 2.86 (m, 1H), 3.07 (m, 1H), 3.23 (m, 1H), 3.32 (m, 1H), 3.84 (m, 1H), 4.90 (m, 1H), 7.20 (m, 5H), 8.16 (m, 1H), 8.28 (d, 1H), 8.70 (m, 1H), 8.99 (m, 2H). MS(ESI): 457 (M+H).  
 15

Step 2:



(90)

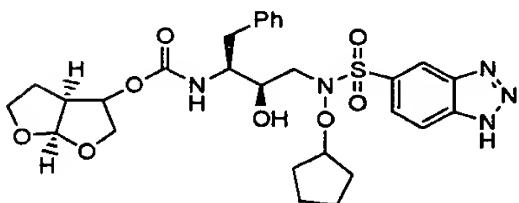
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(3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-benzyl-4-(cyclopentyloxy)-2-hydroxy-4-(6-quinoxalinylsulfonyl)butyl] carbamate. A mixture of (3*R*,4*S*)-4-amino-1-(cyclopentyloxy)-5-phenyl-1-(6-quinoxalinylsulfonyl)-3-pentanol (50 mg, 0.110 mmol), (2*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-2-yl 4-nitrophenyl carbonate (37.3 mg, 0.121 mmol), and *N,N*-diisopropylethylamine (47.8  $\mu\text{L}$ , 0.274 mmol) were combined under an Argon atmosphere in approximately 1.5 mL of

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acetonitrile. After stirring at ambient temperature for 16 hours, the solvent was removed in *vacuo* and the residue was dissolved in ethyl acetate and washed three times with 5% w/v aqueous potassium carbonate. The combined aqueous 5 layers were back-extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated in *vacuo*. The crude product was purified on a preparative TLC plate (20X20 cm, 1000  $\mu$ M) eluting with 95:5 dichloromethane : methanol. 10 The product band was removed, eluted with 3:1 methylene chloride:methanol, filtered, and evaporated in *vacuo*. The residual solid was dried under high vacuum to provide (3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-benzyl-4-(cyclopentyloxy)-2-hydroxy-4-(6- 15 quinoxalinylsulfonyl)butyl]carbamate (53 mg, 79%).  $^1$ H-NMR (chloroform-D3): 1.58 (m, 6H), 1.81 (m, 4H), 2.80 (m, 1H), 2.95 (m, 4H), 3.17 (m, 1H), 3.65 (m, 2H), 3.88 (m, 4H), 4.85 (m, 2H), 4.98 (m, 1H), 5.62 (d, 1H), 7.21 (m, 5H), 8.08 (m, 1H), 8.26 (d, 1H), 8.63 (m, 1H), 9.00 (m, 1H). MS (ESI): 20 613 (M+H).

Example 91



25 (91)

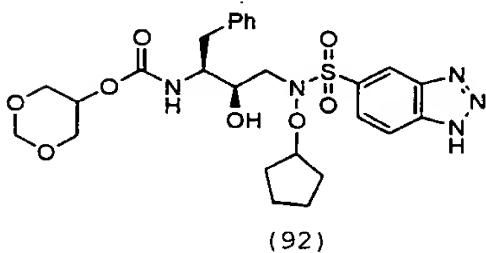
(3*aS*,6*aR*) Hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-[(cyclopentyloxy)(benzotriazole-5-ylsulfonyl)amino]-2-hydroxypropylcarbamate. (3*aS*,6*aR*) Hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-[(cyclopentyloxy)-amino]-2-

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hydroxypropylcarbamate (280 mg, 0.666 mmol) (Step 2, Example 54), benzotriazole-5-sulfonyl chloride (140 mg, 0.666 mmol), and anhydrous diisopropylethylamine (0.04 mL, 0.238 mmol) were combined in anhydrous tetrahydrofuran (5 mL) in a 25 mL 5 round bottomed flask under nitrogen. The reaction was stirred for 24 hours and concentrated in vacuo. After the workup described in Step 3, Example 54, the residue was purified by preparative silica gel TLC using 90:10 chloroform: methanol as an eluent to give the product as a 10 white foam (70 mg, 0.116 mmol, 17%).  $^1\text{H}$ NMR ( $\text{d}_6$ -DMSO)  $\delta$ : 8.42 (bs, 1H), 8.16 (bs, 1H), 7.84 (bs, 1H), 7.26-7.15 (m, 5H), 5.51-5.47 (m, 1H), 5.31-5.28 (m, 1H), 4.85-4.70 (m, 2H), 4.12 (m, 1H), 3.79-1.15 (m, 21H). MS (ES): 602 (M+1), 600 (M-1).

15

Example 92



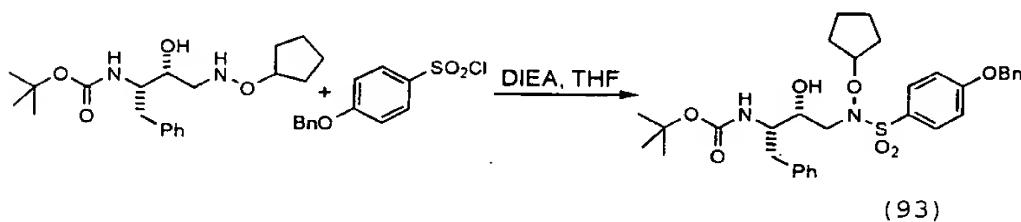
20

1,3-Dioxan-5-yl N-(1S,2R)-1-benzyl-3-[ (cyclopentyloxy) (benzotriazole-5-ylsulfonyl)amino]-2-hydroxypropylcarbamate. 1,3-Dioxan-5-yl N-(1S,2R)-1-benzyl-3-[ (cyclopentyloxy)amino]-2-hydroxypropylcarbamate (Step 1, Example 55), (130 mg, 0.330 mmol), benzotriazole-5-sulfonyl chloride (72 mg, 0.330 mmol), and anhydrous diisopropylethylamine (0.06 mL, 0.330 mmol), were combined in anhydrous tetrahydrofuran (5 mL) in a 25 mL round bottomed flask under nitrogen. The reaction was stirred for 24 hours and concentrated in vacuo. After the workup

described in Step 3, Example 54, the residue was purified by preparative silica gel TLC using 90:10 chloroform: methanol as an eluent to give the product as a white film (56 mg, 0.0973 mmol, 30%).  $^1\text{H}$ NMR ( $\text{d}_6$ -DMSO)  $\delta$ : 8.43 (bs, 1H), 8.14 (m, 1H), 7.83 (m, 1H), 7.27-7.15 (m, 5H), 4.86-4.66 (m, 3H), 4.23-3.02 (m, 13H), 1.93-1.40 (m, 8H). MS(ES): 576 (M+1), 574 (M-1).

Example 93

10



tert-butyl *N*-(1*S*,2*R*)-1-benzyl-3-[(4-(benzyloxy)phenyl)

15 sulfonyl (cyclopentyloxy) amino)-2-hydroxypropylcarbamate.

tert-butyl *N*-(1*S*,2*R*)-1-benzyl-3-[(cyclopentyloxy)amino]-2-

hydroxypropylcarbamate (3.5 mmol, 807 mg), 3-

phenoxybenzenesulfonyl chloride (3.5 mmol, 1.0 g), and

diisopropylethylamine (5.3 mmol, 0.924 mL) were dissolved in

20 anhydrous THF (10 mL), and the solution was stirred at room temperature under nitrogen for 72 hours. The reaction was concentrated to a white solid under vacuum, dissolved in ethyl acetate, washed with 1N HCl, 1N NaOH, brine, dried over magnesium sulfate and concentrated. The crude product

25 was purified by silica gel chromatography (2:1 hexanes/ethyl acetate) and yielded 1.08 g (50%) of a white solid. Note:

The 3-phenoxybenzenesulfonyl chloride was prepared from 4-bromophenylbenzylether (Corrie, J.; Papageorgiou, G. J.

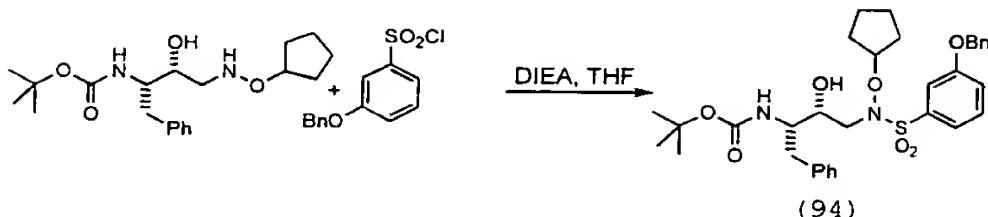
Chem. Soc., Perkin Trans. 1 1996, 1583).  $R_f$  = 0.3 (5:1

30 hexanes/ethyl acetate);  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ):  $\delta$  7.69 (2H, d),

- 204 -

7.41-7.28 (5H, m), 7.27-7.19 (6H, m), 7.03 (2H, d), 5.11 (2H, s), 4.79 (1H, m), 4.56 (1H, m), 3.79 (2H, bs), 3.31 (1H, bs), 3.02 (1H, m), 2.91 (2H, m), 2.79 (1H, m), 1.85-1.67 (4H, m), 1.67-1.43 (4H, m), 1.32 (9H, s).

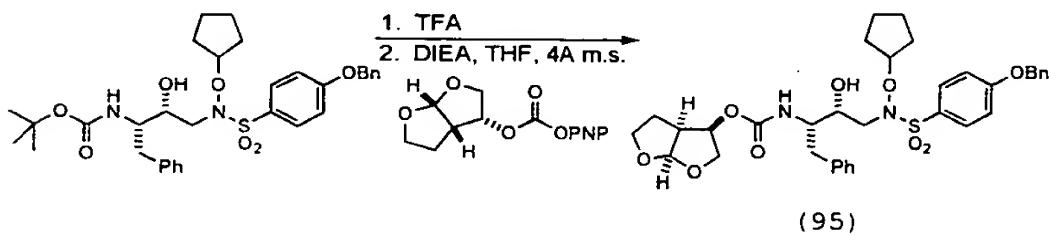
5

Example 94

10 **tert-butyl N-(1*S*,2*R*)-1-benzyl-3-[(3-(benzyloxy)phenyl)sulfonyl (cyclopentyloxy) amino]-2-hydroxypropylcarbamate.** This compound was prepared under the same conditions described for the *tert*-butyl *N*-(1*S*,2*R*)-1-benzyl-3-[(4-(benzyloxy)phenyl)sulfonyl (cyclopentyloxy) amino]-2-hydroxypropylcarbamate.  $R_f = 0.3$  (5:1 hexanes/ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.44-7.30 (8H, m), 7.29-7.16 (7H, m), 5.08 (2H, s), 4.79 (1H, m), 4.53 (1H, m), 3.78 (2H, bs), 3.34 (1H, bs), 3.06 (1H, m), 2.91 (2H, m), 1.85-1.66 (4H, m), 1.66-1.43 (4H, m), 1.32 (9H, s).

15

20

Example 95

25

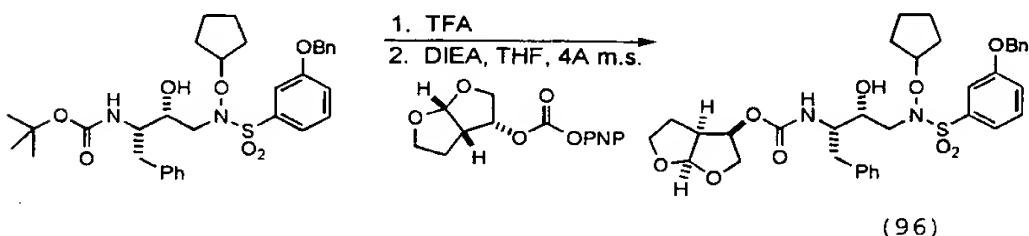
- 205 -

(3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-[(4-(benzyloxy)phenyl)sulfonyl(cyclopentyloxy)amino]-2-hydroxypropylcarbamate. This compound was prepared (from Example 93) under the conditions described for

5 (3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-(cyclohexyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropylcarbamate.  $R_f$  = 0.2 (2:1 hexanes/ethyl acetate); H1-NMR (CDCl<sub>3</sub>):  $\delta$  7.70 (2H,d), 7.44-7.31 (5H,m), 7.29-7.11 (6H,m), 7.05 (2H,d), 5.63 (1H,s), 5.11 (2H,s), 10 5.00 (1H,m), 4.88-4.74 (2H,m), 3.96-3.78 (4H,m), 3.67 (2H,m), 3.08 (1H,bs), 3.05-2.94 (2H,m), 2.90 (2H,m), 2.81 (2H,m), 1.87-1.68 (4H,m), 1.68-1.44 (4H,m).

Example 96

15



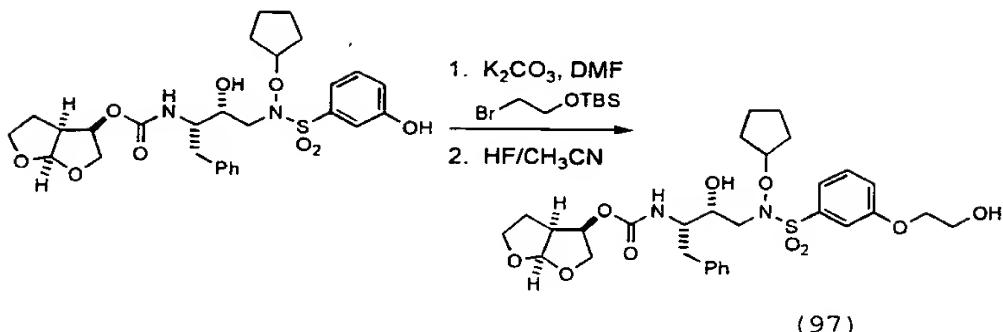
20 (3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-[(3-(benzyloxy)phenyl)sulfonyl(cyclopentyloxy)amino]-2-hydroxypropylcarbamate. This compound was prepared under the conditions (from Example 94) described for (3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-(cyclohexyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropylcarbamate.  $R_f$  = 0.2 (2:1 hexanes/ethyl acetate); H1-NMR (CDCl<sub>3</sub>):  $\delta$  7.48-7.30 (8H,m), 7.30-7.11 (7H,m), 5.59 (1H,s), 5.09 (2H,s), 4.97 (1H,m), 4.78 (2H,m), 3.95-3.77 (4H,m), 3.71-3.57 (2H,m), 3.12 (1H,bs), 3.05-2.90

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(3H, m), 2.90-2.72 (3H, m), 1.88-1.67 (4H, m), 1.67-1.42 (4H, m).

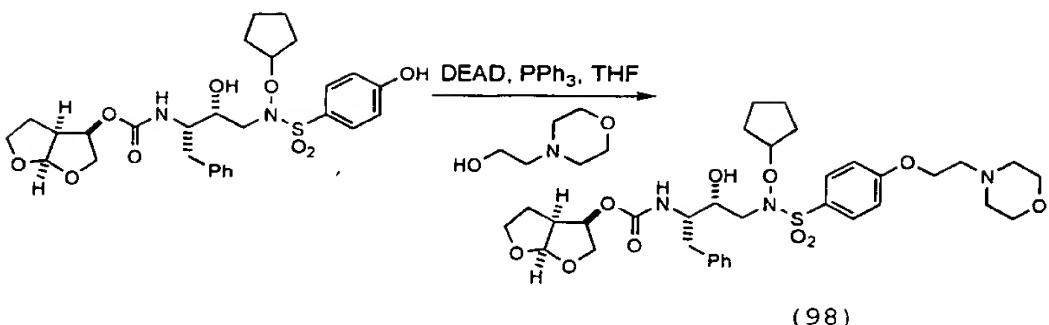
Example 97

5

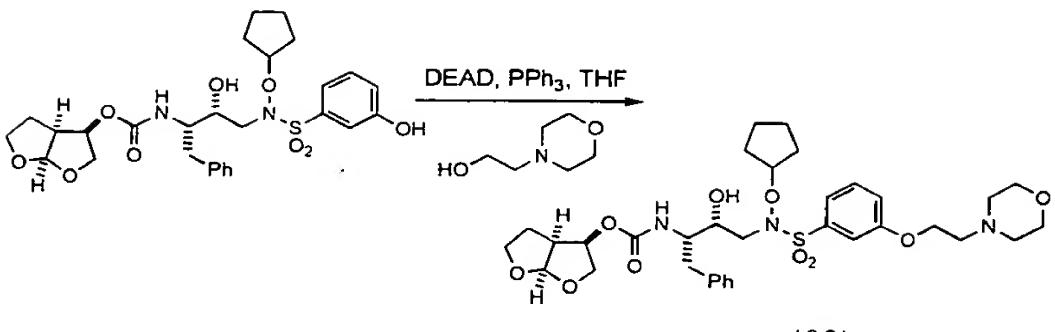


(3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-benzyl-3-((cyclopentyloxy)[3-(2-hydroxyethoxy)phenyl]sulfonylamino)-2-hydroxypropyl]carbamate. This compound was synthesized (from Example 44) under the same conditions as Example 42 (3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-benzyl-3-((cyclopentyloxy)[4-(2-hydroxyethoxy)phenyl]sulfonylamino)-2-hydroxypropyl]carbamate.  $R_f$  = 0.1 (1:1 hexanes/ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.47-7.14 (10H, m), 5.63 (1H, s), 5.00 (1H, m), 4.88-4.70 (2H, m), 4.12 (2H, m), 3.98 (2H, m), 3.94-3.72 (5H, m), 3.72-3.51 (2H, m), 3.14 (1H, bs), 3.07-2.69 (5H, m), 2.20 (1H, bs), 1.89-1.69 (4H, m), 1.69-1.42 (4H, m);  $\text{MS}$  (ESI):  $\text{M}+\text{H}=621$ .

**Example 98**



5 (3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-  
10 benzyl-3-((cyclopentyloxy)[4-(2-morpholinoethoxy)phenyl]sulfonylamino)-2-hydroxypropyl]carbamate. To a solution of (3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-  
15 benzyl-3-(cyclopentyloxy)[(4-hydroxyphenyl)sulfonyl]amino-2-hydroxypropyl]carbamate (Example 41), (0.13 mmol, 75 mg), triphenylphosphine (0.16 mmol, 43 mg), 4-(2-hydroxyethyl)morpholine (0.16 mmol, 0.020 mL), and anhydrous THF (0.5 mL) stirring under nitrogen,  
20 diethylazodicarboxylate (0.17 mmol, 0.027 mL) was injected. The reaction stirred for 3 hours at room temperature and was then concentrated to a viscous oil under vacuum. The crude was purified directly by silica gel flash chromatography (1:1 hexanes/ethyl acetate) resulting in 50 mg (56%) of a white solid.  $R_f$  = 0.15 (ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): δ 7.70 (2H,d), 7.30-7.10 (6H,m), 6.99 (2H,d), 5.63 (1H,s), 5.00 (1H,m), 4.86-4.73 (2H,m), 4.16 (2H,m), 3.97-3.79 (4H,m), 3.78-3.58 (6H,m), 3.15-2.69 (9H,m), 2.57 (4H,m), 1.88-1.66 (4H,m), 1.66-1.43 (4H,m);  $\text{MS}$  (ESI):  $\text{M}+\text{H}=690$ .

Example 99

5

*(3R,3aS,6aR)hexahydrofuro[2,3-*b*]furan-3-yl N-[(1*S*,2*R*)-1-benzyl-3-((cyclopentyloxy)[3-(2-morpholinoethoxy)phenyl]sulfonylamino)-2-hydroxypropyl]carbamate.*

This compound was prepared from Example 44 under the same

10 conditions used for the preparation of Example 98

*(3R,3aS,6aR)hexahydrofuro[2,3-*b*]furan-3-yl N-[(1*S*,2*R*)-1-benzyl-3-((cyclopentyloxy)[4-(2-morpholinoethoxy)phenyl]sulfonylamino)-2-hydroxypropyl]carbamate.*  $R_f = 0.15$

(ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.44-7.14 (10H, m), 5.62

15 (1H, s), 5.00 (1H, m), 4.79 (2H, m), 4.16 (2H, m), 3.98-3.60

(10H, m), 3.12 (1H, bs), 3.02-2.71 (8H, m), 2.58 (4H, m), 1.90-

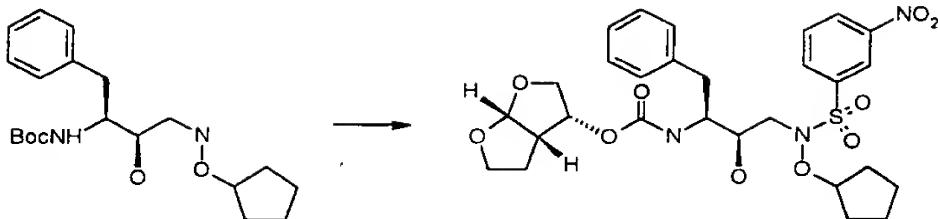
1.72 (4H, m), 1.72-1.42 (4H, m);  $\text{MS}$  (ESI):  $M+H=690$ .

Example 100

20

**Phosphate ester of *(3R,3aS,6aR)hexahydrofuro[2,3-*b*]furan-3-yl N-[(1*S*,2*R*)-3-[(3-aminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate.***

## Step 1:



5 A solution of 0.792g (2.18 mMol) of tert-butyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)amino]-2-hydroxypropylcarbamate (Example 54), 0.445g (2.4 mMol) of m-nitrobenzenesulfonyl chloride and 0.35 mL (2.5 mMol) of triethylamine in 10mL of tetrahydrofuran was stirred at rt for 12h, diluted with

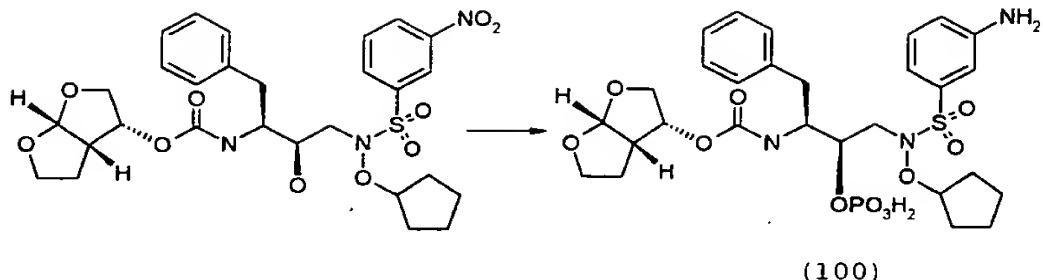
10 ethyl acetate and extracted with 1N HCl and saturated sodium bicarbonate. Purification on silica gel afforded the desired sulfonamide which was treated with 50 mL of 1:1 trifluoroacetic acid/ dichloromethane for 1h at rt. Evaporation of the volatiles and partitioning between ethyl acetate and 1N sodium hydroxide, afforded the free base

15 which was treated with 0.885g (3 mmol) of (3R,3aS,6aR)-hexahydrofuro[2,3-*b*]furan-3-yl (4-nitrophenyl) carbonate, 10 mg of dimethylamino pyridine, and 0.7 mL of triethylamine in 20 mL of tetrahydrofuran for 12h at rt. The resulting

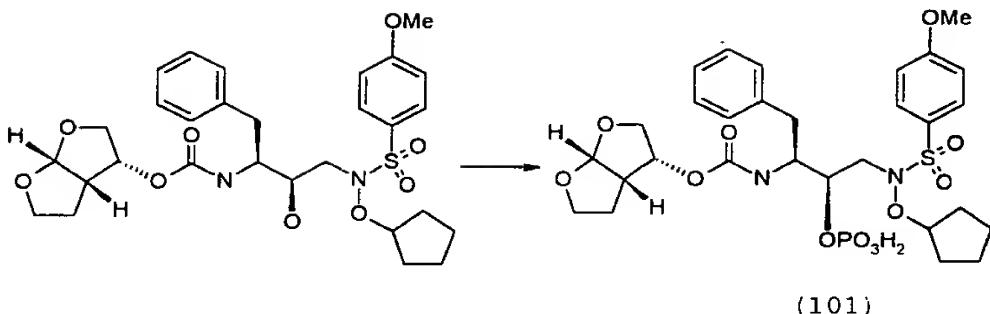
20 mixture was loaded onto a bed of silica gel and eluted with 50% to 100% ethylacetate-hexanes) to give the desired compound (750 mg) as a white foam.

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## Step 2:



5 A solution of 60.5 mg (0.1 mmol) of the material obtained in Step 1 above, 0.042 mL (0.125 mmol) of diisopropylamino-dibenzylphosphite and 9 mg (0.13 mmol) of tetrazole in 2 mL of dichloromethane was stirred for 3 h at rt and then loaded onto a bed of silica gel and eluted with 30% ethylacetate-hexane to give the intermediate phosphite which was re-dissolved in 3 mL of acetonitrile and treated with 48.3 mg (0.15 mmol) of iodosobenzene diacetate. The mixture was stirred at rt for 1h and then loaded on a plug of silica gel and eluted with 80% ethylacetate-hexane. The resulting phosphate ester was obtained as a white foam (48 mg), which was re-dissolved in 50 ml methanol and treated with ca. 50 mg of 5% palladium on carbon. The mixture was hydrogenated at 55PSI for 8h, filtered and evaporated. Purification on C-18 semi-preparative HPLC gave the desired phosphate (6 mg) as a white fluffy solid. <sup>1</sup>H-NMR (methanol-d<sub>4</sub>): 1.4-2.0 (14H), 2.65 (1H), 2.9 (1H), 3.2 (2H), 3.55 (1H), 3.6-4.0 (4H), 4.4 (1H), 4.65 (1H), 4.8 (2H), 5.6 (1H), 7.2-7.6 (9H). <sup>31</sup>P-NMR: 1.1 ppm. MS (LC-MS): 656 (M<sup>+</sup>).

Example 101

5

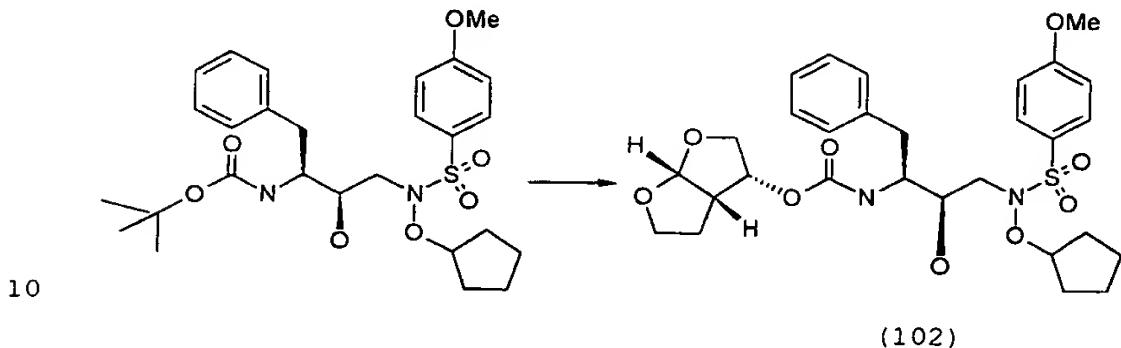
**Phosphate ester of (3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate.** A solution of 0.6 g (1 mmol) of (3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate (Example 102), 0.42 mL (1.25 mmol) of diisopropylamino-dibenzylphosphite and 0.09g (1.25 mmol) of tetrazole in 10 mL of dichloromethane was stirred at rt for 12h. The mixture was loaded onto a plug of silica gel and eluted with 40% ethylacetate-hexane to give the desired phosphite. 250 mg of the material so obtained were dissolved in 15 mL of acetonitrile and treated with 0.19 g (0.6 mmol) of iodosobenzene diacetate. After 2h at rt, the mixture was diluted with ethyl acetate and extracted with 1N HCl and 1N NaOH. The volatiles were removed and the residue was chromatographed on silica gel to give 220 mg of the protected phosphate as a white foam. 100 mg of the so obtained material was dissolved in 20 mL of methanol and treated with ca. 20 mg of 5% palladium on carbon. Hydrogenation at 50 PSI for 1h and filtration gave the desired acid which was dissolved in 2M methanolic ammonia

- 212 -

and re-evaporated. The ammonium salt was isolated as a white solid (65mg).

1H-NMR (methanol-D4): 1.5-2.2 (14H), 2.7 (1H), 2.9 (3H), 3.15 (1H), 3.4-4 (5H), 3.97 (3H), 4.2-4.7 (2H), 4.9 (2H), 5.6 (1H), 7.2 (3H), 7.3 (4H), 7.85 (2H). 31P-NMR: 0.08ppm  
 5 MS (LC-MS): 671 (MH<sup>+</sup>).

Example 102



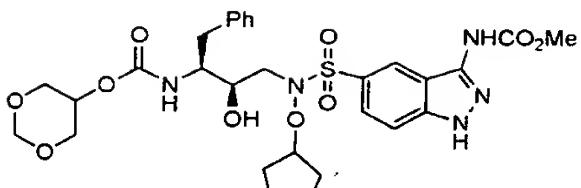
(3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate. This compound was obtained in  
 15 analogous manner to Example 29, using the appropriate optically pure activated carbonate. 1H-NMR (CDCl<sub>3</sub>): 1.4-1.9 (12H), 2.75 (2H), 2.9 (1H), 3.1 (2H), 3.65 (2H), 3.9 (6H), 4.75 (2H), 5.00 (1H), 5.62 (1H), 7.0 (2H), 7.15 (5H), 7.75 (2H).  
 20

Example 103

Prepared as outlined for Example 86, using chiral starting  
 25 materials.

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### Example 104

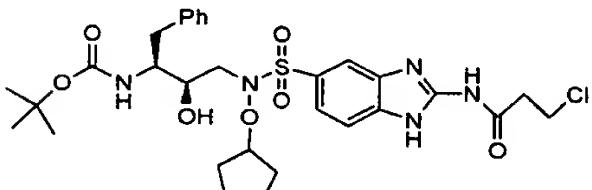


(104)

5

1,3-Dioxan-5-yl-N-(1*S*,2*R*)-1-benzyl-3-[(cyclopentyloxy)(3-(carbomethoxyamino)-indazole-5-ylsulfonyl)amino]-2-hydroxypropylcarbamate. 1,3-Dioxan-5-yl N-(1*S*,2*R*)-1-benzyl-3-[(cyclopentyloxy)(1-carbomethoxy-3-(carbomethoxyamino)indazole-5-ylsulfonyl)amino]-2-hydroxypropylcarbamate (Example 120), (40 mg, 0.057 mmol) and lithium iodide (23 mg, 0.17 mmol) were dissolved in pyridine (3 mL) in a 10 mL round bottomed flask and heated at 95°C for 2 hours. The reaction was allowed to cool and then concentrated in vacuo. The product was purified by preparative silica gel TLC using 90:10 chloroform: methanol as an eluent to yield a beige solid (35 mg, 0.054 mmol, 95 %).  $^1\text{H}$ NMR ( $d_6$ -DMSO)  $\delta$ : 13.12 (s, 1H), 10.26 (s, 1H), 8.42 (s, 1H), 7.62 (m, 2H), 7.25-7.09 (m, 6H), 5.12 (d,  $J=6.2$  Hz, 1H), 4.76-4.18 (m, 5H), 3.76-2.91 (m, 9H), 3.66 (s, 3H), 1.90-1.40 (m, 8H). MS (ES): 648 ( $M+1$ ), 646 ( $M-1$ ).

### Example 105



(105)

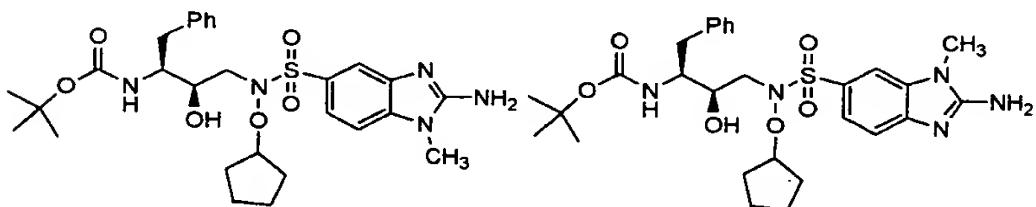
- 214 -

**Tert-butyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)(2-[(3-chloropropionyl)amino]-1H-benzimidazol-5-ylsulfonyl)amino]-2-hydroxypropylcarbamate.** Tert-butyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)(2-amino-1H-benzimidazol-5-ylsulfonyl)amino]-2-hydroxypropylcarbamate (Step 2, Example 8) (65 mg, 0.116 mmol), 3-chloropropionyl chloride (0.01 mL, 0.116 mmol), and 4,4-dimethylaminopyridine were combined in anhydrous THF (5 mL) in a 25 mL round bottomed flask under nitrogen. The reaction was stirred for 18 hours and then 10 concentrated in vacuo. After the workup described in Step 3, Example 54, the residue was purified by preparative silica gel TLC using 10:3:0.5 chloroform: methanol: water as an eluent to give the product as a white solid (17 mg, 0.026 mmol, 22%).  $^1\text{H}$ NMR ( $\text{d}_6$ -DMSO)  $\delta$ : 7.55-6.62 (m, 8H), 5.08 (bs, 1H), 4.62 (bs, 1H), 4.15 (bs, 1H), 3.57 (m, 2H), 3.10-1.40 (m, 16H), 1.18 (s, 9H). MS(ES): 650, 652 (M+1).

Example 106

20 Prepared as outlined in Example 8, Step 2.

Example 107



25

(107)

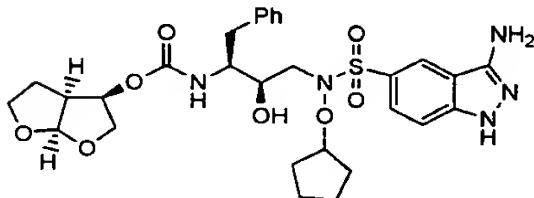
**Tert-butyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)(2-amino-1-methyl-1H-benzimidazol-5-ylsulfonyl)amino]-2-hydroxypropylcarbamate and Tert-butyl N-(1S,2R)-1-benzyl-3-**

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**[(cyclopentyloxy) (2-amino-3-methyl-1H-benzimidazol-5-ylsulfonyl)amino]-2-hydroxypropylcarbamate.** Tert-butyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy) (2-amino-1H-benzimidazol-5-ylsulfonyl)amino]-2-hydroxypropyl-carbamate

5 (Step 2, Example 8) (120 mg, 0.214 mmol), methyl iodide (0.03 mL, 0.429 mmol), and anhydrous diisopropylethylamine (0.07 mL, 0.429 mmol) were combined in anhydrous THF (5 mL) in a 25 mL round bottomed flask under nitrogen. The reaction was heated at reflux for 18 hours and then concentrated in  
10 vacuo. After the workup described in Step 3, Example 54, the residue was purified by preparative silica gel TLC using 90:10 chloroform: methanol as an eluent to give the product as mixture of two compounds methylated at the 1- and 3- positions of the imidazole ring (76 mg, 0.133 mmol, 62%).  
15 LC-MS: 574 (M+1), 572 (M-1).

Example 108



20 (108)

**(3R,3aS,6aR) Hexahydrofuro[2,3-b]furan-3-yl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy) (3-aminoindazole-5-ylsulfonyl)amino]-2-hydroxypropylcarbamate.**

25 (3R,3aS,6aR) Hexahydrofuro[2,3-b]furan-3-yl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy) (1-carbomethoxy-3-aminoindazole-5-ylsulfonyl)amino]-2-hydroxypropylcarbamate (100 mg, 0.148 mmol) and lithium iodide hydrate (50 mg, 0.37 mmol) were dissolved in pyridine (3 mL) in a 10 mL round bottomed flask  
30 and heated at 75 C for 5 hours. The reaction was allowed to

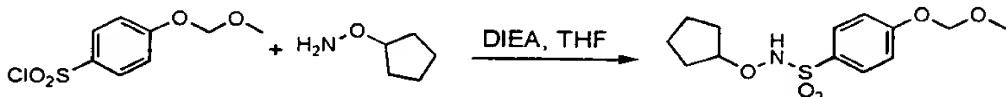
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cool and then concentrated in vacuo. The product was purified by preparative silica gel TLC using 90:10 chloroform: methanol as an eluent to yield a glass (76 mg, 0.124 mmol, 84 %). <sup>1</sup>HNMR (d<sub>6</sub>-DMSO): 12.05 (s, 1H), 8.35 (m, 1H), 7.56-7.14 (m, 7H), 5.86 (bs, 2H), 5.50 (d, J=5.2 Hz, 1H) 5.22 (d, J=6.5 Hz, 1H), 4.85-4.79 (m, 2H), 3.78-1.14 (m, 22H). MS (ES): 616 (M+1), 614 (M-1).

Example 109

10

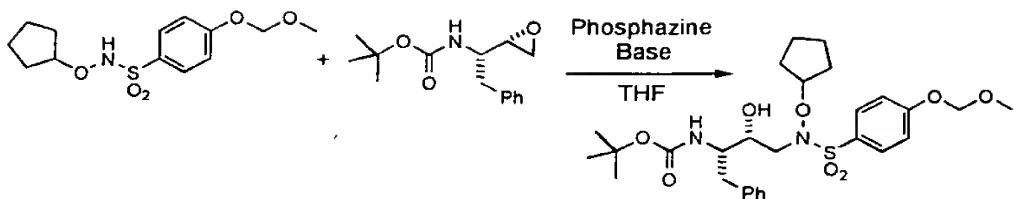
Step 1:



15 **N<sup>1</sup>-(cyclopentyloxy)-4-(methoxymethoxy)-1-benzenesulfonamide**  
 The 4-methoxymethoxybenzenesulfonyl chloride (2.4 mmol, 568 mg) was prepared from methylmethoxy-protected 4-bromophenol (Corrie, J.; Papageorgiou, G. *J. Chem. Soc., Perkin Trans. 1* 1996, 1583) and was combined with cyclopentyl hydroxylamine (2.4 mmol, 243 mg) in the presence of diisopropylethylamine (3.6 mmol, 0.628 mL), and anhydrous THF. The reaction 20 stirred under nitrogen for 36 hours at room temperature and was concentrated under vacuum. The resulting oil was diluted in ethyl acetate, washed with 1N HCl, 5% potassium carbonate, brine and was dried over magnesium sulfate. The crude product was concentrated under vacuum and purified by 25 silica gel chromatography (5:1 hex/ethyl acetate) followed by crystallization from ether/hexanes. The reaction produced 173 mg (24%) of white crystals. R<sub>f</sub> = 0.15 (1:1 hexanes/ethyl acetate); H<sub>1</sub>-NMR (CDCl<sub>3</sub>): δ 7.82 (2H, d), 7.12 (2H, d), 6.67 (1H, s), 5.23 (2H, s), 4.58 (1H, m), 3.47 (3H, s), 1.84-1.64 (4H, m), 1.64-1.43 (4H, m).

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Step 2:

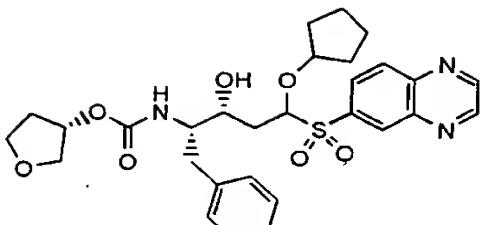


5

**tert-butyl N-((1S,2R)-1-benzyl-3-(cyclopentyloxy)[(4-methoxymethoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate.** *N*<sup>i</sup>-(cyclopentyloxy)-4-methoxymethoxy-1-

10 benzenesulfonamide (0.57 mmol, 173 mg) was combined with tert-butyl *N*-(1*S*)-1-[(2*S*)oxiran-2-yl]-2-phenylethylcarbamate (0.46 mmol, 121 mg) and anhydrous THF (1 mL) under nitrogen. Phosphazine base P<*t*/4>*t*-Bu (0.09 mmol, 0.092 mL, 1M in hexanes) was injected into the stirring solution. The 15 reaction was allowed to stir for 4 hours at room temperature and was quenched by the addition of a few drops of glacial acetic acid. The reaction product was concentrated to an oil and partitioned between ethyl acetate and 1N HCl. The organic layer was separated and washed with 1 N NaOH and 20 brine, dried over magnesium sulfate and concentrated under vacuum to a clear oil. The crude product was purified by silica gel chromatography (5:1 hexanes/ethyl acetate) and crystallization from ether/hexanes providing 110 mg (43%) of a white crystal. *R*<sub>f</sub> = 0.5 (2:1 hexanes/ethyl acetate); *H*1-  
25 NMR (CDCl<sub>3</sub>): 7.69 (2H, d), 7.31-7.16 (6H, m), 7.11 (2H, d), 5.21 (2H, s), 4.83-4.75 (1H, m), 4.61-4.51 (1H, m), 3.85-3.70 (2H, m), 3.47 (3H, s), 3.12-2.95 (1H, m), 2.95-2.87 (2H, m), 2.87-2.68 (1H, m), 1.86-1.66 (4H, m), 1.66-1.43 (4H, m), 1.33 (9H, s); MS (ESI): M+H=565.

30

Example 110

(110)

5

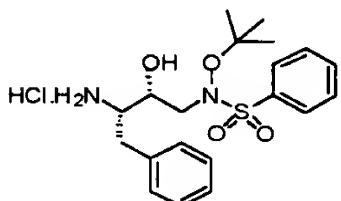
(3*S*) tetrahydro-3-furanyl *N*-[(1*S*,2*R*)-1-benzyl-4-(cyclopentyloxy)-2-hydroxy-4-(6-quinoxalinylsulfonyl)butyl]carbamate. A mixture of (3*R*,4*S*)-4-amino-1-(cyclopentyloxy)-5-phenyl-1-(6-quinoxalinylsulfonyl)-3-pentanol (50 mg, 0.110 mmol), 2,5-dioxo-1-pyrrolidinyl [(3*S*) tetrahydro-3-furanyl] carbonate (28 mg, 0.121 mmol, WO 94/05639) and *N,N*-diisopropylethylamine (47.8  $\mu$ L, 0.274 mmol) were combined under Argon at ambient temperature in approximately 1.5 mL of acetonitrile. After stirring for 10 approximately 16 hours at ambient temperature, the reaction mixture was evaporated in *vacuo* and partitioned between ethyl acetate and aqueous potassium carbonate (5% w/v). The layers were separated and the aqueous layer was back extracted with ethyl acetate. The combined organic layers 15 were washed twice with 1N sodium hydrogen sulfate. The acid layers were combined and back extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated in *vacuo*. The residue was purified on a preparative TLC plate 20 (20X20 cm, 1000  $\mu$ M) eluting with 93:7 dichloromethane:methanol. The product band was removed, eluted with 3:1 methylene chloride: methanol, filtered, and 25 evaporated in *vacuo*. The residue was crystallized with

- 219 -

several drops of methanol. The residual solid was dried under high vacuum to provide (3*S*)tetrahydro-3-furanyl *N*-(*1S,2R*)-1-benzyl-4-(cyclopentyloxy)-2-hydroxy-4-(6-quinoxalinyl sulfonyl)butyl carbamate (54 mg, 86%) as a 5 white solid. *H*1-NMR (chloroform-D3): 1.61 (m, 5H), 1.86 (m, 4H), 2.09 (m, 1H), 2.97 (m, 3H), 3.20 (m, 2H), 3.80 (m, 6H), 4.83 (m, 1H), 4.93 (m, 1H), 5.14 (m, 1H), 7.28 (m, 5H), 8.13 (m, 1H), 8.31 (d, 1H), 8.69 (d, 1H), 9.05 (s, 2H).  
MS (ESI): 571 (M+H).  
10

Example 111

Step 1:

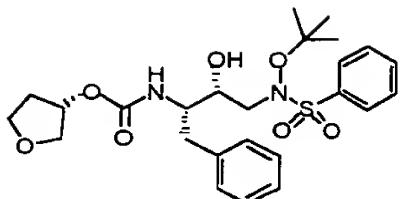


15

(*1S,2R*)-1-benzyl-3-(*tert*-butyloxy)[(phenyl)sulfonyl]amino-2-hydroxypropylamine hydrochloride. *tert*-Butyl-*N*-(*1S,2R*)-1-benzyl-3-(*tert*-butyloxy)[(phenyl)sulfonyl]amino-2-hydroxypropyl carbamate (Example 112, Step 2), (0.060 g, 20 0.12 mmol) was dissolved in EtOAc (50 ml). Dry hydrochloric acid gas was bubbled through the stirred solution 15 minutes at -10 °C. The reaction was warmed to ambient temperature, solvent removed *in vacuo* and the resulting crude residue used directly in the next reaction.

- 220 -

Step 2:



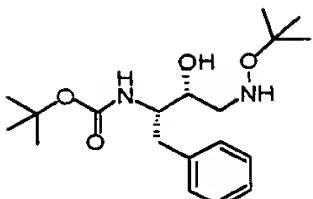
(111)

5 (3S) Tetrahydro-3-furanyl-N-(1S,2R)-1-benzyl-3-(*tert*  
butyloxy)[(phenyl)sulfonyl]amino-2-hydroxypropylcarbamate.  
(1S,2R)-1-benzyl-3-(*tert*-butyloxy)[(phenyl) sulfonyl]amino-  
2-hydroxypropylamine hydrochloride (0.12 mmol) was combined  
with diisopropylethylamine (0.064 ml, 0.37 mmol) in CH<sub>2</sub>Cl<sub>2</sub>  
10 (10 ml). To the reaction was added 2,5-dioxo-1-pyrrolidinyl  
[(3S) tetrahydro-3-furanyl] carbonate (0.042g, 0.18 mmol)  
with stirring. After 3 h at ambient temperature, the  
reaction mixture was concentrated *in vacuo*, taken up in  
EtOAc, washed with sat. aq. NaHCO<sub>3</sub>, and brine. The organic  
15 phase was dried over MgSO<sub>4</sub>, filtered and solvent removed *in vacuo*.  
Purification by preparative TLC (1:1 EtOAc/Hex).  
Recovered 0.044 g (67%) of the product as a white foam. R<sub>f</sub>=  
0.38 (1:1 EtOAc/Hex), LRMS (M+H)<sup>+</sup> 507.3.

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Example 112

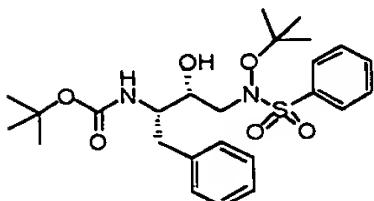
Step 1:



5

**tert-Butyl-N-((1S,2R)-1-benzyl-3-(tert-butyloxyl)amino-2-hydroxypropyl)carbamate.** *tert-Butyl-N-((1S)-1-[(2S)oxiranyl]-2-phenylethylcarbamate* (0.155 g, 0.59 mmol) and *O*-(*tert*-butyl)hydroxylamine hydrochloride (0.089 g, 0.71 mmol) were heated with diisopropylethylamine (0.154 ml, 0.88 mmol) in isopropanol (2 ml) in a sealed tube at 60°C for 5 days. The reaction mixture was concentrated *in vacuo*, taken up in EtOAc, washed with sat. aq. NaHCO<sub>3</sub>, and brine. The organic phase was dried over MgSO<sub>4</sub>, filtered and solvent removed *in vacuo*. Purification by column chromatography (1% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) gave 100 mg of a white solid which was used directly in the next reaction.

Step 2:



20

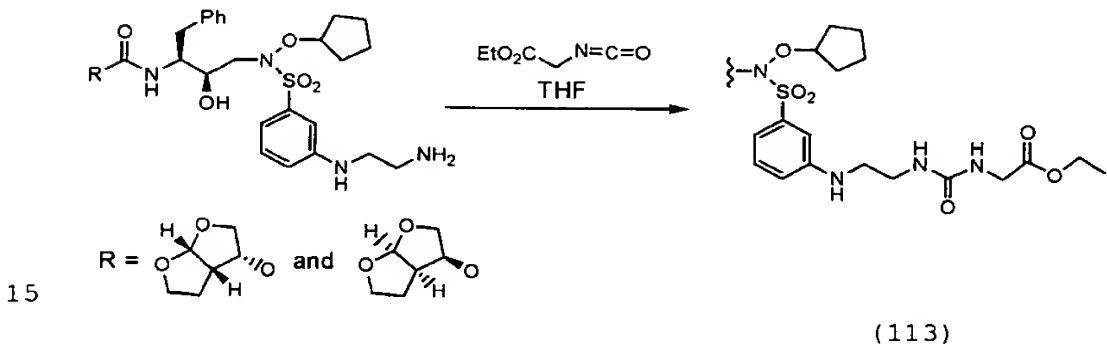
(112)

**tert-Butyl-N-((1S,2R)-1-benzyl-3-(tert-butyloxyl)[(phenyl)sulfonyl]amino-2-hydroxypropyl)carbamate.**

- 222 -

tert-Butyl-N-((1*S*,2*R*)-1-benzyl-3-(tert-butyloxy)amino-2-hydroxypropyl)carbamate (0.100 g, 0.28 mmol) was combined with diisopropylethylamine (0.075 ml, 0.43 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml). Benzenesulfonyl chloride (0.060 g, 0.34 mmol) was 5 added and the reaction was stirred at room temperature overnight. Reaction mixture was concentrated *in vacuo*, taken up in EtOAc, washed with sat. aq. NaHCO<sub>3</sub>, and brine. The organic phase was dried over MgSO<sub>4</sub>, filtered and solvent removed *in vacuo*. Purification by preparative TLC 10 (1:1/EtOAc/Hex). Recovered 0.064 g (46%) of the product as a white foam. R<sub>f</sub> = 0.78 (1:1/EtOAc/Hex), LRMS (M+H)<sup>+</sup> 493.4.

Example 113



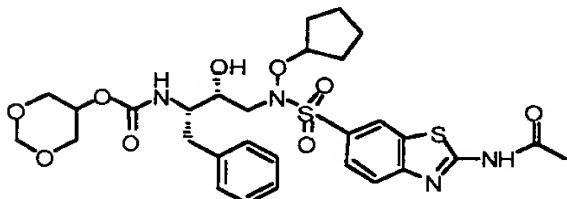
Ethyl 2-[(2-((3-((2*R*,3*S*)-3-((3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl)oxy)carbonylamino)-2-hydroxy-4- 20 phenylbutyl](cyclopentyloxy)amino]sulfonylanilino)ethyl]aminocarbonyl)amino]acetate and ethyl 2-[(2-((3-((2*R*,3*S*)-3-((3*S*,3*aR*,6*aS*)hexahydrofuro[2,3-*b*]furan-3-yl)oxy)carbonylamino)-2-hydroxy-4 phenylbutyl](cyclopentyloxy)amino]sulfonylanilino)ethyl]aminocarbonyl)amino]acetate. 25 A solution of 50 mg (0.081 mmol) of a 1:1 mixture of (3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(3-[(2-aminoethyl)amino]phenylsulfonyl) (cyclopentyloxy)amino]-

- 223 -

1-benzyl-2-hydroxypropylcarbamate and (3*S*, 3a*R*, 6a*S*) hexahydrofuro[2, 3-*b*]furan-3-yl *N*-(1*S*, 2*R*)-3-[(3-[(2-aminoethyl)amino]phenylsulfonyl)(cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate (Example 83) in 1.5 mL of anhydrous THF was treated with 0.010 mL (0.085 mmol) of ethyl isocyanatoacetate. The resulting solution was stirred at RT. After 18 hours the solution was concentrated *in vacuo* and the residue subjected to flash chromatography (silica gel, 95:5/CH<sub>2</sub>Cl<sub>2</sub>/2M NH<sub>3</sub>, in MeOH) to afford 56 mg (92%) of the desired product as a white foam. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.60-7.06 (13H), 6.00-4.80 (4H), 4.34-2.62 (19H), 2.10-1.43 (10H), 1.32 (3H). LCMS(ESI): 748 (M+H).

Example 114

15



(114)

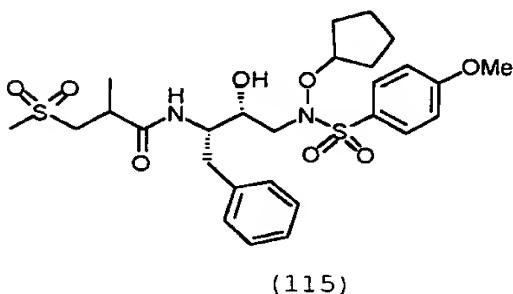
1,3-Dioxane-5-yl *N*-(1*S*, 2*R*)-1-benzyl-3-[(cyclopentyloxy)(2-acetamido)]-benzothiazol-6-ylsulfonyl)amino]-2-hydroxypropylcarbamate. To 21 mg (0.034 mmol) of 1,3-Dioxane-5-yl *N*-(1*S*, 2*R*)-1-benzyl-3-[(cyclopentyloxy)(2-amino)]-benzothiazol-6-ylsulfonyl)amino]-2-hydroxypropylcarbamate, (Example 125, Step 3), dissolved in 1 mL of dichloromethane and cooled to approximately 0°C, was added 5.3 μL (1.2 eq.) of chlorotrimethylsilane. The reaction was warmed to 25°C and stirred for 45 minutes. Triethylamine (12 μL, 2.5 eq.) was added followed by 100 μL (1.2eq.) of a dilute solution of (24 μL acetyl chloride in 1

- 224 -

mL CH<sub>2</sub>Cl<sub>2</sub>). The reaction was stirred at 25°C for 3 hours. 105 µL (3.0 eq.) of 1.0 M tetrabutylammonium fluoride was added and the reaction stirred for 1 hour. The solvent was removed *in vacuo* and the residue was purified by preparative chromatography to give 8 mg of carbamate, 114. HPLC showed the material to be over 80% pure. Ret. time = 10.48 min. LC/MS, M+H = 649.1.

Example 115

10



(115)

1N-(3-Methylsulfonylisobutyryl)-(1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[4-methoxyphenylsulfonyl]amino-2-hydroxypropylamine. (1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropylamine trifluoroacetic acid salt (0.012 g, 0.03 mmol) was combined with 3-methylsulfonylisobutyric acid (0.005 g, 0.03 mmol) and 1-hydroxybenzotriazole hydrate (0.004 g, 0.03 mmol) in anhydrous DMF (1 ml). Triethylamine (0.010 ml, 0.05 mmol) was added followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.009 g, 0.03 mmol). Reaction was stirred at room temperature for 2 hours. Reaction mixture was diluted in EtOAc and washed with sat. NaHCO<sub>3</sub>, 0.5N KHSO<sub>4</sub> and brine. Organic phase was dried with MgSO<sub>4</sub> and the solvent was removed *in vacuo*. Purification by preparative TLC (3:1/EtOAc/Hex). Recovered 0.010 g (70%) of

- 225 -

the product as a colorless residue.  $R_f = 0.44$  (3:1 EtOAc/Hex).  $^1H$  NMR ( $CDCl_3$ ) 8.78 (1H, d), 7.38-7.17 (5H, m), 7.05-6.98 (2H, m), 6.09 (0.5H, d), 5.98 (0.5H, d), 5.80 (1H, m), 4.32 (0.5H, m), 4.20 (0.5H, m), 4.02 (0.5H, m), 3.90 (3H, s), 3.60 (0.5H, m), 3.49 (1H, m), 3.12-2.96 (2H, m), 2.95-2.70 (4H, m), 1.90-1.70 (4H, m), 1.69-1.50 (4H, m), 1.20 (1.5H, d), 1.00 (1.5H, d). LRMS ( $M+H$ )<sup>+</sup> 583.0.

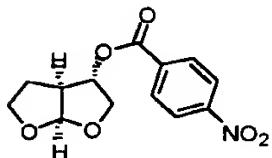
Example 116

10

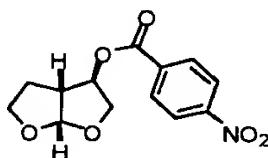
Step 1:

**(3*S*,3a*S*,6a*R*)hexahydrofuro[2,3*b*]furan-3-p-nitrobenzoyl ester (A) and (3*R*,3a*R*,6a*S*)hexahydrofuro[2,3*b*]furan-3-p-nitrobenzoyl ester (B)**

15



(A)



(B)

In a dried flask was introduced 1 eq. of  
 20 (3*S*,3a*S*,6a*R*)-3-Hydroxyhexahydrofuro[2,3*b*] furan (200 mg, 1.54 mmol) in 10 mL of dried THF. To this solution was introduced 1.1 eq. of  $PPh_3$  (443 mg, 1.69 mmol) and 1.1 eq. of *p*-nitrobenzoic acid (282 mg, 1.69 mmol). The solution was cooled to 0°C and then 1.2 eq of diethyl azodicarboxylate (290  $\mu$ L, 1.84 mmol) was added dropwise. The reaction was continued at room temperature for 24 h. The solvent was evaporated in *vacuo* to an oil which was solubilized in dichloromethane washed with 1N hydrochloric acid, saturated sodium bicarbonate and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated in  
 25  
 30

- 226 -

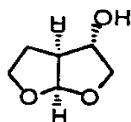
vacuo to a residue. The crude material was purified on flash grade silica gel eluting with 20-50% ethyl acetate in hexane. Fractions containing the product were combined, evaporated in vacuo and dried under high vacuum to provide  
5 (3*S*,3a*S*,6a*R*)Hexahydrofuro [2,3*b*]furan-3-p-nitrobenzoyl ester (914 mg, 98%). HPLC showed the material to be 98% pure; Ret. time = 9.88 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 8.14-8.24 (dd, 4H), 5.88 (d, 1H), 5.29 (s, 1H), 4.07-4.17 (m, 2H), 3.83-3.93 (m, 2H), 2.97 (m, 1H), 2.19-2.28 (m, 1H), 1.86-1.98 (m, 1H).

10

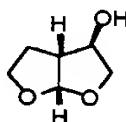
Step 2:

(3*S*,3a*S*,6a*R*)-3-Hydroxyhexahydrofuro[2,3*b*]furan (C) and (3*R*,3a*R*,6a*S*)-3-Hydroxyhexahydrofuro[2,3*b*]furan (D)

15



(C)



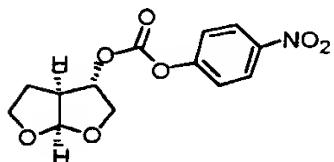
(D)

In a flask was introduced 1 eq. of (3*R*,3a*R*,6a*S*)Hexahydrofuro [2,3*b*]furan-3-p-nitrobenzoyl ester (1.34 g, 4.82 mmol) in 20 mL of methanol. To this solution was introduced at room temperature 1 eq. of lithium hydroxide (202 mg, 4.82 mmol). After 45 min the solvant was evaporated in vacuo to an oil who was purified on flash grade silica gel eluting with 50-100% ethyl acetate in hexane. Fractions containing the product were combined, evaporated in vacuo and dried under high vacuum to provide (3*R*,3a*R*,6a*S*)-3-Hydroxyhexahydrofuro [2,3*b*]furan (401 mg, 80%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 5.82 (s 1H), 4.15 (s, 1H), 3.74-3.94 (m, 4H), 2.72-2.76 (m, 1H), 2.06-2.14 (m, 1H), 1.99 (s, 1H), 1.60-1.66 (m, 1H).

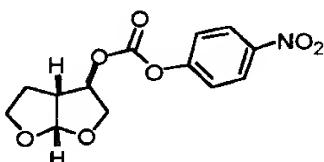
- 227 -

Step 3:

(3*S*,3*aS*,6*aR*) Hexahydrofuro[2,3*b*]furan-3-yl (4-nitrophenyl) carbonate (E) and (3*R*,3*aR*,6*aS*) hexahydrofuro[2,3*b*]furan-3-yl (4-nitrophenyl) carbonate (F)



(E)

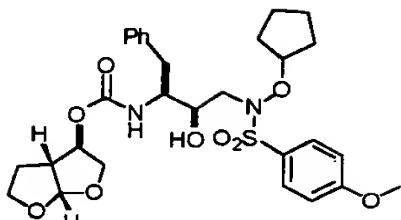


(F)

10 In a dried flask was introduced 1 eq. of (3*S*,3*aS*,6*aR*)-3-Hydroxy hexahydrofuro[2,3*b*]furan (210 mg, 1.61 mmol) in 5 mL of dried dichloromethane. To this solution was introduced 1 eq. of *p*-nitrobenzylchloroformate (325 mg, 1.61 mmol) and 1 eq. of *N*-methylmorpholine (177  $\mu$ L, 1.61 mmol). The reaction 15 was continued at room temperature for 24 h. The precipitate was filtered off and the solvant was evaporated in vacuo to an oil. The crude material was purified on flash grade silica gel eluting with 50% ethyl acetate in hexane. Fractions containing the product were combined, evaporated 20 in vacuo and dried under high vacuum to provide (3*S*,3*aS*,6*aR*) Hexahydrofuro[2,3*b*]furan-3-yl (4-nitrophenyl) carbonate (350 mg, 99%). HPLC showed the material to be 99% pure; Ret. time = 8.8 min.  $^1$ H NMR ( $CDCl_3$ ): 7.28-8.25 (dd, 4H), 5.88 (d, 1H), 5.05 (s, 1H), 4.04-4.15 (m, 2H), 3.80-25 3.91 (m, 2H), 2.97-3.01 (m, 1H), 2.18-2.26 (m, 1H), 1.77-1.83 (m, 1H).

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## Step 4:



(116)

5

(3*R*,3a*R*,6a*S*)hexahydrofuro[2,3b]furan-3-yl-N-((1*S*,2*R*)-1-benzyl-3-[(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl]carbamate. In a dried flask was introduced 1 eq. of *N*<sup>1</sup>-[(2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl]-*N*<sup>1</sup>-(cyclopentyloxy)-4-methoxy-1-benzenesulfonamide trifluoroacetic acid (40.9 mg, 0.083 mmol) in 1 mL of *N,N*-dimethylformamide. To this solution was added 1.1 eq. of (3*R*,3a*R*,6a*S*)hexahydrofuro [2,3b]furan-3-yl-(4-nitrophenyl) carbonate (27 mg, 0.091 mmol) and 5 eq. of triethylamine (58  $\mu$ L, 0.4 mmol). The reaction was continued at room temperature for 4 days. The reaction mixture was solubilized in ethyl acetate washed with water and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated in vacuo to a residue. The crude material was purified on a preparative TLC plate (20x20 cm, 1 mm) eluting with 50% ethyl acetate in hexane. The product band was removed, eluted (4:1/dichloromethane:methanol), filtered and evaporated in vacuo and dried under high vacuum to provide (3*S*,3a*S*,6a*R*)Hexahydrofuro [2,3b]furan-3-yl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate (19.5 mg, 40%). HPLC showed the material to be 96% pure; Ret. time = 11.88 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.65 (d, 2H), 7.13-7.24 (m, 5H), 6.92 (d, 2H), 5.71 (m, 1H), 4.73-4.82 (m, 3H), 3.71-3.91 (m, 7H), 2.68-3.03 (m,

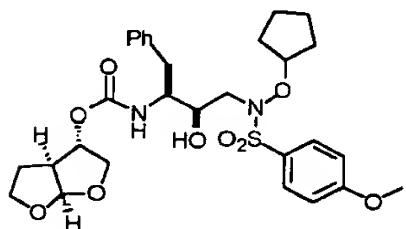
- 229 -

7 H), 2.12 (m, 1H), 1.48-1.74 (m, 10H) and MS (ES+), M+H = 591.0.

Example 117

5

(3*S*,3a*S*,6a*R*)hexahydrofuro[2,3b]furan-3-yl-N-((1*S*,2*R*)-1-benzyl-3-[(cyclopentyloxy) [(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropylcarbamate



10

(117)

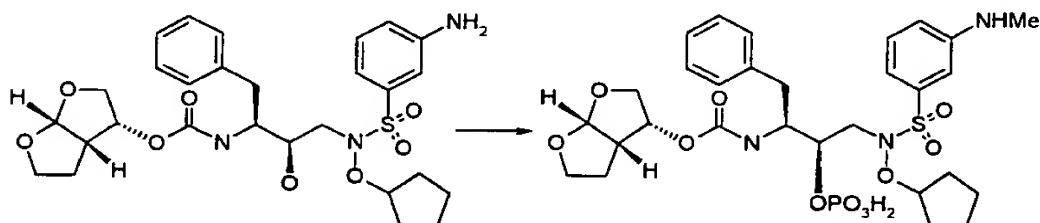
In a dried flask was introduced 1 eq. of *N*<sup>1</sup>-((2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutyl)-*N*<sup>1</sup>-(cyclopentyloxy)-4-methoxy-1-benzenesulfonamide•trifluoroacetic acid (40.2 mg, 0.081 mmol) in 1 mL of *N,N*-dimethylformamide. To this solution was added 1.1 eq. of (3*S*,3a*S*,6a*R*)hexahydrofuro[2,3b]furan-3-yl (4-nitrophenyl) carbonate (26 mg, 0.089 mmol) and 5 eq. of triethylamine (56  $\mu$ L, 0.4 mmol). The reaction was continued at room temperature for 4 days. The reaction mixture was solubilized in ethyl acetate washed with water and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated in vacuo to a residue. The crude material was purified on a preparative TLC plate (20x20 cm, 1 mm) eluting with 50% ethyl acetate in hexane. The product band was removed, eluted (4:1/dichloromethane:methanol), filtered and evaporated in vacuo and dried under high vacuum to provide (3*S*,3a*S*,6a*R*)Hexahydrofuro[2,3b]furan-3-yl *N*-((1*S*,2*R*)-1-

- 230 -

benzyl-3-(cyclopentyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropylcarbamate (18.4 mg, 38%). HPLC showed the material to be 96% pure; Ret. time = 11.8 min.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.65 (d, 2H), 7.13-7.24 (m, 5H), 6.92 (d, 2H), 5.71 (m, 1H), 4.73-4.82 (m, 3H), 3.71-3.91 (m, 7H), 2.68-3.03 (m, 7 H), 2.12 (m, 1H), 1.48-1.74 (m, 10H) and MS (ES $^+$ ),  $\text{M}+\text{H} = 591.0$ .

Example 119

10



(119)

**Phosphate ester of (3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-**

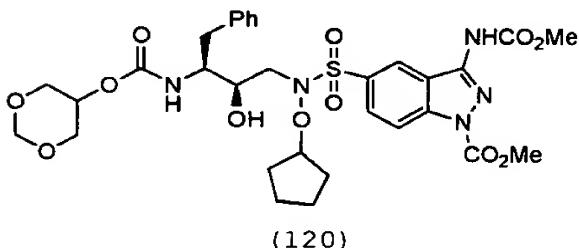
15 **yl  $N$ -(1*S*,2*R*)-3-[(3-N-methylaminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate.**  
 A solution of 0.145g (0.25 mMol) of (3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl  $N$ -(1*S*,2*R*)-3-[(3-N-aminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate (Example 77), 0.042 mL (0.3 mMol) of triethylamine and 0.081g (0.3 mMol) of 2,4-dinitrobenzenesulfonyl chloride in 2 mL of tetrahydrofuran was treated with 0.2 mL of pyridine and 0.03 g of 4-N,N-dimethylamino pyridine and stirred at rt overnight. The mixture was diluted with ethylacetate and extracted with 1N HCl and saturated sodium bicarbonate. Chromatography on silica gel (1:1 ethyl acetate-hexanes) gave 75mg of a yellow foam which was dissolved in 1 mL of dimethylformamide and treated with 0.03 mL of iodomethane and 0.06 mL of

- 231 -

triethylamine. The resulting mixture was heated to 70°C for 10h and then evaporated. Chromatography on silicagel (40% ethylacetate-hexanes) gave a white foam which was dissolved in 1mL of acetonitrile and 1 mL of dichloromethane. This 5 solution was treated with 0.06 mL of dibenzyldiisopropyl phosphoramidite and 0.02g of tetrazole. The resulting solution was stirred at rt for 0.5 h and evaporated. Chromatography on silicagel (40% ethylacetate - hexanes) gave a colorless oil which was dissolved in 1 mL of 10 acetonitrile and 1 mL of dichloromethane and treated with 0.2g of iodosobenzene diacetate. After two hours at rt, the volatiles were removed and the residue was re-dissolved in dichloromethane. The solution was treated with 1.5 mL of n-propylamine for 15 minutes and then evaporated. 15 Chromatography on silicagel (60% ethylacetate - hexanes) gave a yellow oil which was dissolved in 20 mL of 2M ammonia in methanol and treated with 5 mg of 5% palladium on carbon. The mixture was hydrogenated for 1 h at 50 PSI, filtered and evaporated to give 15 mg of a white powdery solid. <sup>1</sup>H NMR 20 (CD<sub>3</sub>CN): 1.5-1.9 (13H), 2.75 (1H), 2.8-3.0 (3H), 2.90 (3H), 3.15 (1H), 3.7 (1H), 3.9 (5H), 4.8 (1H), 5.0 (1H), 5.5 (1H), 7.0-7.4 (7H), 7.5 (2H). <sup>31</sup>P NMR (CD<sub>3</sub>CN): 2.1 ppm). LC-MS: 671 (MH<sup>+</sup>).

Example 120

25



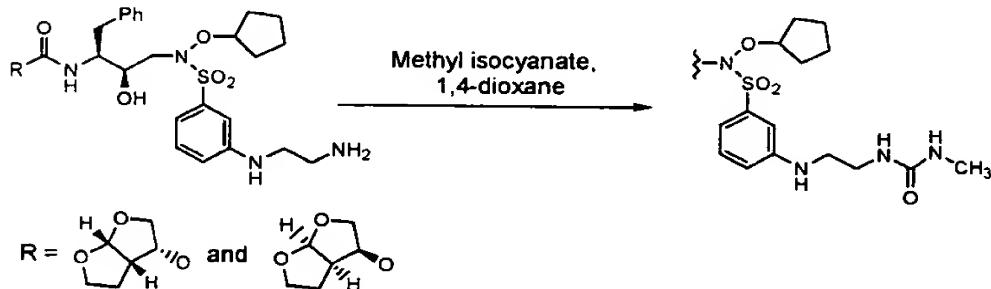
1,3-Dioxan-5-yl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)(1- 30 carbomethoxy-3-(carbomethoxyamino)indazole-5-

- 232 -

ylsulfonyl)amino]-2-hydroxypropylcarbamate. 1,3-Dioxan-5-yl N-(1*S*,2*R*)-1-benzyl-3-[(cyclopentyloxy)amino]-2-hydroxypropylcarbamate (Step 1, Example 55), (130 mg, 0.330 mmol), 1-carbomethoxy-3-(carbomethoxyamino)indazole-5-sulfonyl chloride (110 mg, 0.330 mmol), and anhydrous diisopropylethylamine (0.06 mL, 0.330 mmol), were combined in anhydrous tetrahydrofuran (5 mL) in a 25 mL round bottomed flask under nitrogen. The reaction was stirred for 24 hours and concentrated in vacuo. After the workup described in Step 3, Example 54, the residue was purified by preparative silica gel TLC using 3:1/ethyl acetate:hexane as an eluent to give the product as a oil (91 mg, 0.129 mmol, 39%).  $^1\text{H}$ NMR ( $d_6$ -DMSO): 10.99 (s, 1H), 8.73 (s, 1H), 8.35 (d,  $J=8.9$  Hz, 1H), 7.95 (d,  $J=8.9$  Hz, 1H), 7.27-7.16 (m, 5H), 5.24 (d,  $J=6.5$  Hz, 1H), 4.85-4.63 (m, 3H), 4.06 (s, 3H), 3.80-3.00 (m, 11H), 3.76 (s, 3H), 1.97-1.40 (m, 8H). MS(ES): 706 (M+1), 704 (M-1).

Example 121

20



(3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl N-(1*S*,2*R*)-1-benzyl-3-[(cyclopentyloxy)(3-[(2-[(methylamino)carbonyl]aminoethyl)amino]phenylsulfonyl)amino]-2-hydroxypropylcarbamate and (3*S*,3a*R*,6a*S*) hexahydrofuro[2,3-

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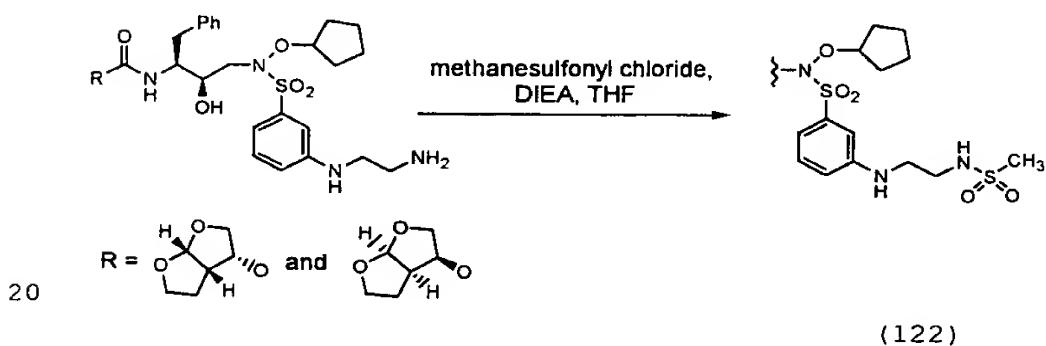
**b] furan-3-yl N-(1S,2R)-1-benzyl-3-[ (cyclopentyloxy) (3-[ (2-[(methylamino) carbonyl]amino ethyl)amino]phenylsulfonyl)amino]-2-hydroxypropylcarbamate.**

A solution of 33 mg (0.053 mmol) of a 1:1 mixture of

5 (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl N-(1S,2R)-3-[ (3-[ (2-aminoethyl)amino]phenylsulfonyl) (cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate and (3S,3aR,6aS)hexahydrofuro[2,3-b]furan-3-yl N-(1S,2R)-3-[ (3-[ (2-aminoethyl)amino]phenylsulfonyl) (cyclopentyloxy)amino]-10 1-benzyl-2-hydroxypropylcarbamate (Example 83) in 1 mL of anhydrous 1,4-dioxane was treated with 0.003 mL (0.05 mmol) of methyl isocyanate. The resulting solution was stirred at RT. After 2 hours the solution was concentrated *in vacuo* to afford 35 mg (97%) of the desired product as a white foam.

15 1H-NMR (CDCl<sub>3</sub>): 7.43-7.01 (13H), 5.76-4.80 (4H), 4.08-2.70 (18H), 1.90-1.30 (10H). LCMS (ESI): 676 (M+H).

**Example 122**

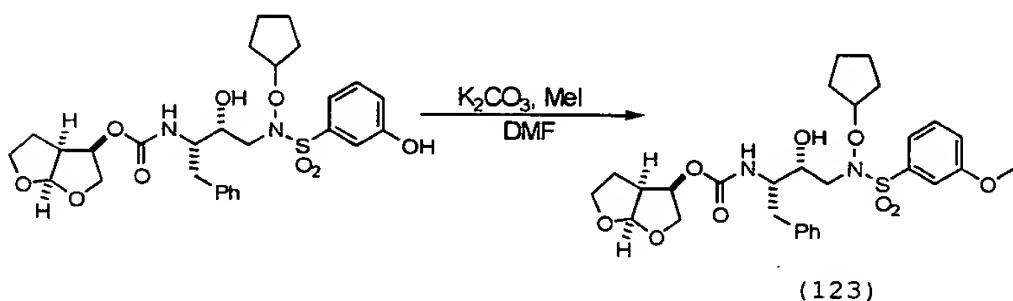


25 **(3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl N-[ (1S,2R)-1-benzyl-3-[ (cyclopentyloxy) [3-(2-[(methylsulfonyl) amino]ethylamino]phenylsulfonyl]amino]-2-hydroxypropyl]carbamate and (3S,3aR,6aS)hexahydrofuro[2,3-b]furan-3-yl N-[ (1S,2R)-1-benzyl-3-[ (cyclopentyloxy) [3-(2-**

- 234 -

[(methylsulfonyl)amino]ethylamino)phenyl]sulfonylamino)-2-hydroxypropyl]carbamate. A solution of 33 mg (0.053 mmol) of a 1:1 mixture of (3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(3-[(2-aminoethyl)amino]phenylsulfonyl) 5 (cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate and (3*S*,3a*R*,6a*S*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(3-[(2-aminoethyl)amino]phenylsulfonyl)(cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate (Example 83) in 2 mL of anhydrous THF at 0°C was treated with 0.010 mL (0.059 mmol) 10 of *N,N*-diisopropylethylamine followed by 0.005 mL (0.06 mmol) of methanesulfonyl chloride. The resulting solution was allowed to warm to RT with stirring. After 3 hours the solution was concentrated *in vacuo* and the residue subjected to flash chromatography (silica gel, 95:5 CH<sub>2</sub>Cl<sub>2</sub>/2M NH<sub>3</sub> in 15 MeOH) to afford 31 mg (86%) of the desired product as a white foam. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.40-6.81 (12H), 5.62 (1H), 5.43-5.04 (1H), 4.99 (1H), 4.81 (1H), 3.97-2.60 (18H), 1.90-1.30 (10H). LCMS (ESI): 697 (M+H).

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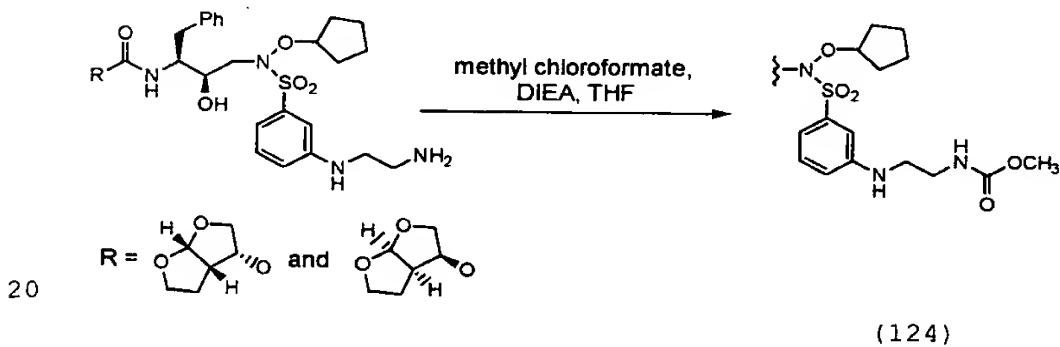
Example 123

25 (3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-[(cyclopentyloxy) [(3-methoxyphenyl)sulfonyl]amino]-2-hydroxypropyl]carbamate

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(3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(3-hydroxyphenyl)sulfonyl]amino-2-hydroxypropyl]carbamate was combined with potassium carbonate (0.86 mmol, 120 mg), iodomethane (0.86 mmol, 0.054 mL), and anhydrous DMF (0.5 mL) under nitrogen. The reaction stirred for 3 hours at 50°C and was concentrated to an oil under vacuum, diluted in ethyl acetate, washed with distilled water and brine, and dried over magnesium sulfate. The crude reaction product was concentrated and purified by 10 silica gel chromatography (1:1/hexanes/ethyl acetate) and yielded 51 mg (>99%) of a fine white powder.;  $R_f$  = 0.15 (1:1 hexanes/ethyl acetate);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.46-7.39 (1H, m), 7.38-7.32 (1H, m), 7.32-7.13 (8H, m), 5.65-5.60 (1H, m), 5.03-4.94 (1H, m), 4.84-4.71 (2H, m), 3.95-3.84 (5H, m), 3.84 (3H, s), 3.70-3.61 (2H, m), 3.13 (1H, bs), 3.06-2.72 (5H, m), 1.87-1.69 (4H, m), 1.70-1.54 (4H, m); MS (ESI):  $M+H=591$ .

Example 124

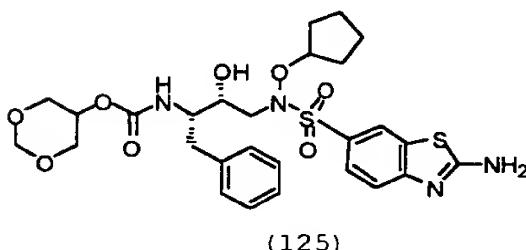


(3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[3-(2-[(methoxycarbonyl)amino]ethylamino)phenylsulfonyl]amino]-2-hydroxypropyl]carbamate and (3*S*,3*aR*,6*aS*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[3-(2-

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**[(methoxycarbonyl)amino]ethylamino)phenyl]sulfonylamino)-2-hydroxypropyl]carbamate.** A solution of 33 mg (0.053 mmol) of a 1:1 mixture of (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl N-(1S,2R)-3-[(3-[(2-aminoethyl)amino]phenylsulfonyl) (cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate and (3S,3aR,6aS)hexahydrofuro[2,3-b]furan-3-yl N-(1S,2R)-3-[(3-[(2-aminoethyl)amino]phenylsulfonyl) (cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate (Example 83) in 2 mL of anhydrous THF at 0°C was treated with 0.010 mL (0.059 mmol) 5 of *N,N*-diisopropylethylamine followed by 0.005 mL (0.06 mmol) of methyl chloroformate. The resulting solution was allowed to warm to RT with stirring. After 3 hours the solution was concentrated *in vacuo* and the residue subjected to flash chromatography (silica gel, 95:5 CH<sub>2</sub>Cl<sub>2</sub>/2M NH<sub>3</sub> in 10 MeOH) to afford 32 mg (89%) of the desired product as a white foam. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.40-6.81 (12H), 5.61 (1H), 5.40-4.87 (2H), 4.80 (1H), 3.97-2.63 (18H), 1.90-1.30 (10H). LCMS (ESI): 677 (M+H). 15

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Example 125

(125)

25 **Preparation of 1,3-Dioxane-5-yl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy) (2-amino)]-benzothiazol-6-ylsulfonyl]amino)-2-hydroxypropylcarbamate**

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Step 1:

To a suspension of 2-aminobenzothiazole (4 g, 26.6 mmol) in 20 mL of dichloromethane under nitrogen was added 4 mL of anhydrous DMF. The solution was cooled to -5°C and 5 triethylamine (7.4 mL, 53.2 mmol, 2.0 eq.) was added. Methanesulfonyl chloride (2.3 mL, 29.3 mmol, 1.1 eq.) was added over 5 minutes followed by an additional 4 mL of dichloromethane. The reaction was warmed to 25°C. After approximately 24 hours at 25°C, the reaction was quenched 10 with saturated bicarbonate solution and partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with water (4X), saturated brine solution, dried over sodium sulfate, filtered and the solvent removed *in vacuo* 15 to give 930 mg of a residue that was shown by LCMS to contain almost no product. The combined aqueous layers were extracted with excess ethyl acetate. These organic layers were washed with saturated brine solution, dried over sodium sulfate, filtered and the solvent removed *in vacuo* 20 to give 1.2 g of product that was shown by HPLC and LCMS to be over 97% pure desired product which was used without further purification. LCMS: 229.0 (M+H).

Step 2:

25 To 2.4 mL (35 mmol, 20 eq.) of chlorosulfonic acid, stirred under nitrogen at -40°C, was added 2-methane-sulfonamidobenzothiazole (Step 1) (400 mg, 1.75 mmol) in small portions over 10 minutes. The suspension was stirred at -40°C for 5 minutes, then was warmed to 0°C for 2.5 30 hours, then warmed to 25°C. After approximately 4 days at 25°C, the reaction was quenched by adding dropwise to well stirred ice water. A small amount of solid was filtered off and shown by HPLC to contain only a small amount of the

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desired product. The aqueous layer was extracted with ethyl acetate (2x) and the combined organic layers were washed with saturated brine solution, dried over sodium sulfate, filtered and the solvent removed *in vacuo* to give 146 mg of 5 the desired material. HPLC showed the material to be ~80% pure, Ret. time = 9.42 min. The material was used without further purification.

Step 3:

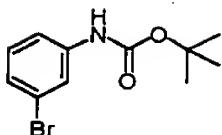
10 To 64 mg (.26 mmol) of 2-aminobenzothiazole-6-sulfonyl chloride, (2), was added 102 mg (.26 mmol, 1.0 eq.) of 1,3-Dioxane-5-yl N-(1S,2R)-1-benzyl-3-(cyclopentyloxyamino)2-hydroxypropylcarbamate (Example 55, Step 1) and 7 mg of 4-dimethylaminopyridine. The mixture was dissolved in 3 mL of 15 anhydrous pyridine to give a yellow solution. Solid formed within 5 minutes and the suspension stirred at 25°C, under nitrogen, for approximately 21 hours. The reaction was quenched with saturated sodium bicarbonate solution and ethyl acetate. The solvent removed *in vacuo* to remove 20 excess pyridine, and the residue was extracted with ethyl acetate (2x). The combined organic layers were washed with saturated brine solution, dried over sodium sulfate, filtered and the solvent was removed *in vacuo* to give 100 mg of 25 2-aminobenzothiazole-6-sulfonyl chloride, (2). HPLC showed the material to be 94% pure, Ret. time = 8.343 min. The material was used without further purification.

<sup>1</sup>H NMR (chloroform-D3) 5.71 (s, 2H), 8.62 (d, 1H), 7.95 (d, 1H), 8.29 (s, 1H) and LC/MS, M+H = 248.9 confirms no methanesulfonyl group present.

30

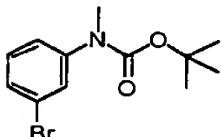
Example 126

Step 1:



**3-Bromo-N-tert-butoxycarbonylaniline.** 3-Bromoaniline (0.50 ml, 4.6 mmol) di-tert-butyldicarbonate (1.20 g, 5.5 mmol) and 4-dimethylaminopyridine (0.003 g) were combined in anhydrous  $\text{CH}_2\text{Cl}_2$  (10 ml). Solution chilled to 0°C and triethylamine (1.28 ml, 9.2 mmol) was added. Reaction was allowed to warm to room temperature then was heated to reflux for 1 hour. Reaction mixture was diluted in  $\text{EtOAc}$  and washed with sat.  $\text{NaHCO}_3$ , 0.5N  $\text{KHSO}_4$  and brine. Organic phase was dried with  $\text{MgSO}_4$  and the solvent was removed in vacuo. Purification by flash chromatography (1:4/ $\text{EtOAc}/\text{Hex}$  to 1:3 to 1:2). Recovered 1.01 g (81%) of the product as a light yellow solid.  $\text{R}_f=0.62$  (1:4  $\text{EtOAc}/\text{Hex}$ ).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 7.68 (1H, s), 7.22-7.10 (3H, m), 6.48 (1H, b), 1.51 (9H, s).

Step 2:

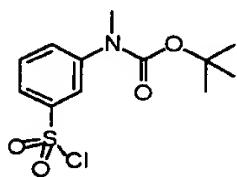


**3-Bromo-N-tert-butoxycarbonyl-N-methylaniline.** 3-Bromo-N-tert-butoxycarbonylaniline (0.50 g, 1.8 mmol) was dissolved in anhydrous DMF (5 ml). Sodium hydride (0.088 g, 2.2 mmol) was added to the solution and the deprotonation was stirred 10 minutes at room temperature. Methyl iodide (0.137 ml, 2.2 mmol) was added slowly and the reaction was stirred overnight at room temperature. Reaction mixture was diluted

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in EtOAc and washed with H<sub>2</sub>O and brine. The organic phase was dried with MgSO<sub>4</sub> and the solvent was removed in vacuo to give 0.51 g (96%) of the product cleanly as a light yellow oil. R<sub>f</sub>=0.63 (1:4 EtOAc/Hex). <sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.41 5 (1H, s), 7.30 (1H, m), 7.20 (2H, m), 3.23 (3H, s), 1.49 (9H, s).

Step 3:



10

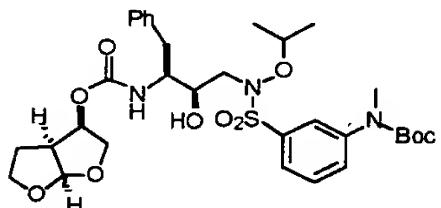
**N-tert-Butoxycarbonyl-3-chlorosulfonyl-N-methylaniline.** 3-Bromo-N-tert-butoxycarbonyl-N-methylaniline (0.358g, 1.2 mmol) was dissolved in freshly distilled THF (5 ml) under a N<sub>2</sub> atmosphere. The solution was chilled to -78°C and n-butyl lithium (0.750 ml, 2.0 M solution in cyclohexane, 1.5 mmol) was added. After 15 minutes, sulfonyl chloride (0.121 ml, 1.5 mmol) was added and the reaction was allowed to warm to room temperature and stirring was continued overnight. THF was removed by evaporation and the resulting residue was diluted in EtOAc. Organic phase was washed with H<sub>2</sub>O and brine before being dried with MgSO<sub>4</sub>. The solvent was removed in vacuo. Purification by flash chromatography (1:19/EtOAc/Hex gradient to 1:9 and then to 1:4). Recovered 15 0.089 g (23%) of the product as a colorless oil. R<sub>f</sub>=0.14 mmol) was added and the reaction was allowed to warm to room temperature and stirring was continued overnight. THF was removed by evaporation and the resulting residue was diluted in EtOAc. Organic phase was washed with H<sub>2</sub>O and brine before being dried with MgSO<sub>4</sub>. The solvent was removed in vacuo. Purification by flash chromatography (1:19/EtOAc/Hex gradient to 1:9 and then to 1:4). Recovered 0.089 g (23%) of the product as a colorless oil. R<sub>f</sub>=0.14 20 25 30 0.089 g (23%) of the product as a colorless oil. R<sub>f</sub>=0.14 (1:9 EtOAc/Hex). <sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.96 (1H, s), 7.80 (1H, d), 7.68 (1H, d), 7.57 (1H, t), 3.33 (3H, s), 1.50 (9H, s).

Step 4:

**(3R,3aS,6aR) Hexahydrofuro[2,3b]furan-3-yl-N-(1S,2R)-1-30 benzyl-3-[ (isopropoxy) [(3-(N-(methyl-tert-**

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**Butoxycarbonyl)phenyl sulfonyl]amino-2-hydroxypropylcarbamate**



5

(126)

In a dried flask was introduced 1 eq. of (3*R*,3a*S*,6a*R*) Hexahydrofuro[2,3*b*]furan-3-yl-N-(1*S*,2*R*)-1-benzyl-3-[(isopropoxy) amino]-2-hydroxypropylcarbamate (53.6 mg, 0.14 mmol) in 2 mL of dried pyridine. To this solution was added 1.2 eq. of *N*-tert-Butoxycarbonyl-3-chlorosulfonyl-*N*-methylaniline (50 mg, 0.16 mmol) and catalytic amount of *N,N*-dimethyl aminopyridine. The reaction was continued at room temperature for 24 h. The solvent was evaporated in vacuo to an oil who was solubilized in ethyl acetate washed with 1N hydrochloric acid, and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated in vacuo to a residue. The crude material was purified on flash grade silica gel eluting with 50% ethyl acetate in hexane. Fractions containing the product were combined, evaporated in vacuo and dried under high vacuum to provide (3*R*,3a*S*,6a*R*) Hexahydrofuro[2,3*b*]furan-3-yl-N-(1*S*,2*R*)-1-benzyl-3-[(isopropoxy) [(3-(*N*-(methyl-*tert*-Butoxycarbonyl)phenyl)sulfonyl]amino-2-hydroxypropylcarbamate (29.2 mg, 31%). HPLC showed the material to be 98% pure; Ret. time = 12.1 min. <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.09-7.78 (m, 9H), 5.56 (d, 1H), 5.15 (bs, 1H), 4.91 (q, 1H), 4.49 (q, 1H), 3.57-3.88 (m, 5H), 3.24 (s, 3H), 2.96 (m, 2H), 2.72 (m,

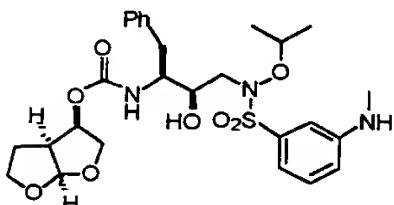
- 242 -

1H), 2.56 (m, 1H), 1.42-1.50 (m+s, 13H), 1.19 (d, 6H) and LCMS (ES+), M+H = 664.3.

Example 127

5

**(3R,3aS,6aR) Hexahydrofuro[2,3b]furan-3-yl-N-(1S,2R)-1-benzyl-3-[(isopropoxy) [(3-N-methylphenyl)sulfonyl]amino-2-hydroxypropylcarbamate**



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(127)

In a dried flask was introduced 1 eq. of (3R,3aS,6aR) Hexahydrofuro[2,3b]furan-3-yl-N-(1S,2R)-1-benzyl-3-[(isopropoxy) [(3-(N-(methyl-tert-Butoxycarbonyl))phenyl)sulfonyl]amino-2-hydroxy propylcarbamate (10.8 mg, 0.016 mmol) in 1 mL dichloromethane. To this solution was added 600  $\mu$ L of trifluoroacetic acid. The reaction was continued at room temperature for 45 min. The solvent was evaporated in vacuo to an oil. The crude material was purified on flash grade silica gel eluting with 50% ethyl acetate in hexane. Fractions containing the product were combined, evaporated in vacuo and dried under high vacuum to provide (3R,3aS,6aR) Hexahydrofuro[2,3b]furan-3-yl-N-(1S,2R)-1-benzyl-3-[(isopropoxy) [(3-N-methylphenyl)sulfonyl]amino-2-hydroxypropyl carbamate (7.2 mg, 78%). HPLC showed the material to be 98% pure; Ret. time = 10.1 min.  $H^1$ -NMR (CDCl<sub>3</sub>): 7.09-7.35 (m, 9H), 6.86 (m, 1H), 5.58 (d, 1H), 4.92-4.96 (m, 2H), 4.46-4.50 (m, 2H), 3.56-3.85 (m, 5H),

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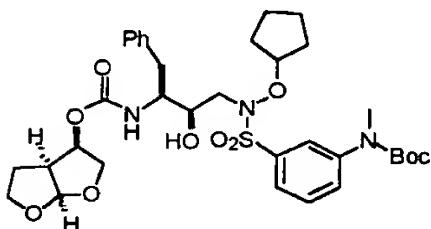
2.71-2.97 (m+s, 7H), 1.45-1.80 (m, 3H), 1.17 (d, 6H) and LCMS (ES+), M+H = 564.3.

Example 128

5

(3*R*,3a*S*,6a*R*) hexahydrofuro[2,3*b*]furan-3-yl-N-(1*S*,2*R*)-1-benzyl-3-[(cyclopentyloxy)[(3-(*N*-(methyl-*tert*-Butoxycarbonyl))phenyl) sulfonyl]amino-2-hydroxypropylcarbamate

10



(128)

In a dried flask was introduced 1 eq. of (3*R*,3a*S*,6a*R*) Hexa hydrofuro[2,3*b*]furan-3-yl-N-(1*S*,2*R*)-1-benzyl-3-

15 [(cyclopentyloxy) amino]-2-hydroxypropylcarbamate (60 mg, 0.14 mmol) in 2 mL of dried pyridine. To this solution was added 1.3 eq. of *N*-*tert*-Butoxycarbonyl-3-chlorosulfonyl-*N*-methylaniline (57 mg, 0.19 mmol) and catalytic amount of *N,N*-dimethylaminopyridine. The reaction was continued at 20 room temperature for 24 h. The solvent was evaporated in vacuo to an oil which was solubilized in ethyl acetate washed with 1N hydrochloric acid, and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated in vacuo to a residue. The crude material was 25 purified on flash grade silica gel eluting with 50% ethyl acetate in hexane. Fractions containing the product were combined, evaporated in vacuo and dried under high vacuum to provide (3*R*,3a*S*,6a*R*) hexahydrofuro[2,3*b*]furan-3-yl-N-(1*S*,2*R*)-1-benzyl-3-[(cyclopentyloxy)[(3-(*N*-(methyl-*tert*-

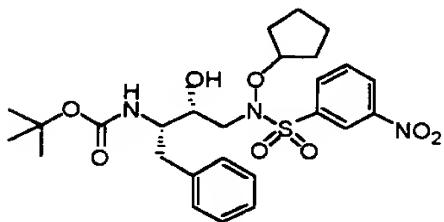
- 244 -

Butoxycarbonyl)phenyl) sulfonyl]amino-2-hydroxypropylcarbamate (26.8 mg, 28%). HPLC showed the material to be 99% pure; Ret. time = 12.88 min.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ): 7.74 (m, 1H), 7.09-7.51 (m, 9H), 5.60 (m, 1H), 5.25 (bs, 1H), 4.94 (q, 1H), 4.77 (q, 1H), 3.71-3.86 (m, 6H), 3.52 (m, 1H), 3.24 (m, 3H), 3.08 (m, 1H), 2.85-2.93 (m, 4H), 2.68 (m, 1H), 1.73-1.83 (m, 5H), 1.42-1.59 (m+s, 12H) and LCMS (ES+),  $\text{M}+\text{H} = 690.2$ .

10

Example 129

Step 1:



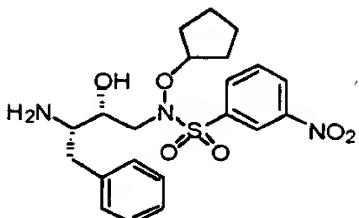
**tert-Butyl-N-((1S,2R)-1-benzyl-3-(cyclopentyloxy)amino-2-hydroxypropyl)carbamate.**

15  $\text{tert-Butyl-N-((1S,2R)-1-benzyl-3-(cyclopentyloxy)amino-2-hydroxypropyl)carbamate}$  (0.52 g, 1.4 mmol) was combined with 3-nitrobenzenesulfonyl chloride (0.47 g, 2.1 mmol) in freshly distilled THF (5 ml). Diisopropylethylamine (0.74 ml, 4.3 mmol) was added and the reaction was stirred at room 20 temperature overnight. Reaction mixture was diluted in EtOAc and washed with 0.5 N  $\text{KHSO}_4$ , and brine. Organic phase was dried with  $\text{MgSO}_4$  and solvent was removed *in vacuo*. Purification by flash chromatography (1:4/EtOAc/Hex gradient to 1:3, to 1:2, to 1:1 and then to 2:1). Recovered 0.44 g 25 (56%) of the product as a white foam.  $\text{R}_f = 0.45$  (2:1 EtOAc/Hex),  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ) 8.67 (1H, s), 8.49 (1H, d), 8.08 (1H, d), 7.77 (1H, t), 7.36-7.17 (5H, m), 4.88 (1H, m), 4.62 (1H, b), 3.88-3.71 (2H, m), 3.41 (1H, b), 3.07 (1H, b), 2.98-

- 245 -

2.79 (3H, m), 1.92-1.75 (4H, m), 1.73-1.52 (4H, m), 1.45 (9H, s).

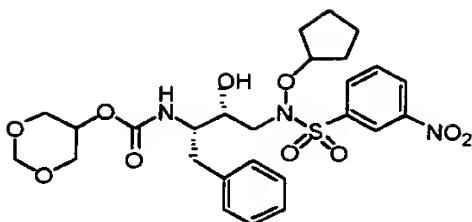
Step 2:



5

(1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)-(3-nitrophenyl)sulfonyl]amino-2-hydroxypropylamine. *tert*-Butyl-N-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)-(3-nitrophenyl)sulfonyl) amino-2-hydroxypropyl carbamate (0.34 g, 0.6 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (3 ml). Trifluoroacetic acid was added with stirring and the reaction was stirred 15 minutes at room temperature. The solvent was removed by evaporation and the resulting residue was partitioned between EtOAc and sat.  $\text{NaHCO}_3$ . Organic phase was washed with sat.  $\text{NaHCO}_3$  and brine then dried with  $\text{MgSO}_4$ . Solvent was removed in vacuo to give 0.27 g (100%) of the product as a white foam.  $R_f$  = 0.11 (2:1 EtOAc/Hex).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 8.75 (1H, s), 8.52 (1H, d), 8.19 (1H, d), 7.80 (1H, t), 7.40-7.08 (5H, m), 4.90 (1H, m), 3.80 (1H, m), 3.36-3.14 (2H, m), 3.05 (1H, b), 2.88 (1H, d), 2.48 (1H, m), 1.96-1.75 (4H, m), 1.74-1.50 (4H, m).

Step 3:

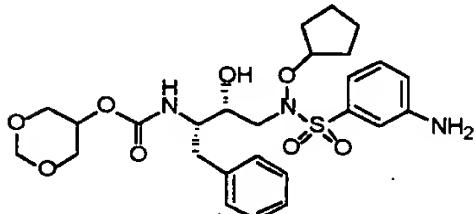


1,3-Dioxan-5-yl-N-(1*S*,2*R*)-benzyl-3-(cyclopentyloxy)[(3-nitrophenyl)sulfonyl]amino-2-hydroxypropylcarbamate.

(1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(3-

5 nitrophenyl)sulfonyl]amino-2-hydroxypropylamine (0.070 g, 0.2 mmol) was combined with 1,3-dioxan-5-yl-(4-nitrophenyl)carbonate (0.066g, 0.2 mmol) in anhydrous DMF (4 ml) under a N<sub>2</sub> atmosphere. Triethyl amine (0.045 ml, 0.3 mmol) was added and the reaction was stirred at room  
10 temperature for 2 hours. Reaction mixture was diluted in EtOAc and washed with sat. NaHCO<sub>3</sub>, 0.5N KHSO<sub>4</sub> and brine. The organic phase was dried with MgSO<sub>4</sub> and solvent was removed *in vacuo*. Purification by flash chromatography (1:2 EtOAc/Hex to 1:1 to 2:1). Recovered 0.073 g (78%) of the  
15 product as a white foam. R<sub>f</sub> = 0.26 (1:1 EtOAc/Hex). <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.66 (1H, s), 8.50 (1H, d), 8.08 (1H, d), 7.77 (1H, t), 7.36-7.13 (5H, m), 5.01 (1H, d), 4.92 (1H, d), 4.88 (1H, m), 4.73 (1H, d), 4.50 (1H, s), 4.00-3.79 (6H, m), 3.13 (1H, m), 3.08-2.88 (2H, m), 2.77 (1H, m), 1.96-1.73 (4H, m),  
20 1.72-1.52 (4H, m).

Step 4:



(129)

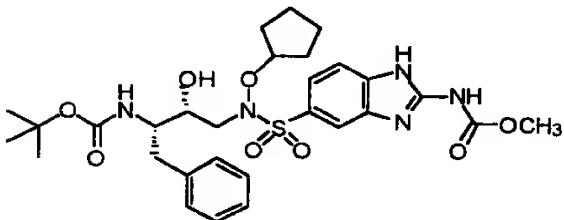
- 247 -

**1,3-Dioxan-5-yl-N-(1*S*,2*R*)-benzyl-3-(cyclopentyloxy)[(3-aminophenyl)sulfonyl]amino-2-hydroxypropylcarbamate.**

1,3-Dioxan-5-yl-N-(1*S*,2*R*)-benzyl-3-(cyclopentyloxy)[(3-nitrophenyl)sulfonyl]amino-2-hydroxypropylcarbamate (0.070

5 g, 0.1 mmol) was combined with tin chloride dihydrate (0.109 g, 0.5 mmol) in absolute ethanol (10 ml). Reaction was heated to reflux and stirred for 2.5 hours. Ethanol was removed *in vacuo* and the material was purified by preparative TLC (2:1/EtOAc/Hex). Recovered 0.045 g (68%) of 10 the product as a colorless residue.  $R_f$  = 0.36 (2:1 EtOAc/Hex).  $^1H$  NMR ( $CDCl_3$ ) 7.38-7.18 (6H, m), 7.15 (1H, d), 7.07 (1H, s), 6.85 (1H, d), 5.00 (1H, d), 4.92 (1H, d), 4.83 (1H, m), 4.76 (1H, d), 4.53 (1H, s), 4.05-3.80 (5H, m), 3.73 (1H, m), 3.19 (1H, m), 3.10 (1H, m), 3.00-2.82 (2H, m), 1.91-15 1.70 (4H, m), 1.69-1.50 (4H, m). LRMS ( $M+H$ )<sup>+</sup> 550.3.

Example 130



20 (130)

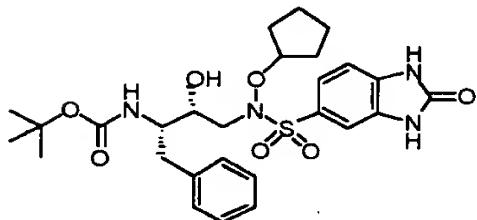
**tert-Butyl-N-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)(2-(methoxycarbonyl)amino)benzimidazol-5-ylsulfonyl)amino-2-hydroxypropylcarbamate.** *tert*-Butyl-N-((1*S*,2*R*)-1-benzyl-3-25 (cyclopentyloxy)amino-2-hydroxypropyl)carbamate (step 1, Example 54), (0.75 g, 2.1 mmol) was combined with 2-(methoxycarbonyl)amino benzimidazol-5-ylsulfonyl chloride (0.89g, 3.1 mmol) in anhydrous DMF (15 ml) under a  $N_2$

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atmosphere. Diisopropylethylethyl amine (1.08 ml, 6.2 mmol) was added and the reaction was stirred at room temperature for 24 hours. The reaction mixture was diluted in EtOAc and washed with sat. NaHCO<sub>3</sub>, 0.5N KHSO<sub>4</sub> and brine. Organic phase was dried with MgSO<sub>4</sub> and solvent was removed in vacuo. Purification by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub> to 1% MeOH in CH<sub>2</sub>Cl<sub>2</sub> to 2% to 3% to 4%). Recovered 0.79 g (62%) of product as a white foam. R<sub>f</sub> = 0.08 (3% MeOH/CH<sub>2</sub>Cl<sub>2</sub>). HPLC t<sub>R</sub> = 10.47 min (C18 column). LRMS (M+H)<sup>+</sup> 618.2.

10

Example 131



(131)

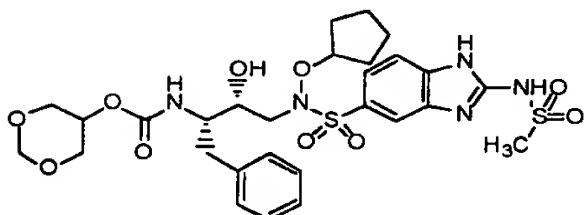
15

**tert-Butyl-N-((1S,2R)-1-benzyl-3-(cyclopentyloxy)(2-hydroxybenzimidazol-5-ylsulfonyl)amino-2-hydroxypropyl)carbamate.** *tert-Butyl-N-((1S,2R)-1-benzyl-3-(cyclopentyloxy)amino-2-hydroxypropyl)carbamate* (Step 1, Example 54), (0.100 g, 0.3 mmol) was combined with 2-oxobenzimidazol-5-ylsulfonyl chloride (0.070 g, 0.3 mmol) in anhydrous DMF (2 ml) under a N<sub>2</sub> atmosphere. Diisopropylethylethyl amine (1.08 ml, 6.2 mmol) was added and the reaction was stirred at room temperature overnight. The reaction mixture was diluted in EtOAc and washed with sat. NaHCO<sub>3</sub>, 0.5N KHSO<sub>4</sub> and brine. Organic phase was dried with MgSO<sub>4</sub> and solvent was removed in vacuo. Purification by flash chromatography (1:1/EtOAc/Hex to 2:1 to 3:1 to

- 249 -

EtOAc). Recovered 0.052 g (54%) of product as a white foam. Rf= 0.10 (2:1 EtOAc/Hex). HPLC t<sub>R</sub>=10.08 min (C18 column). LRMS (M+H)<sup>+</sup> 561.2.

5

Example 132

(132)

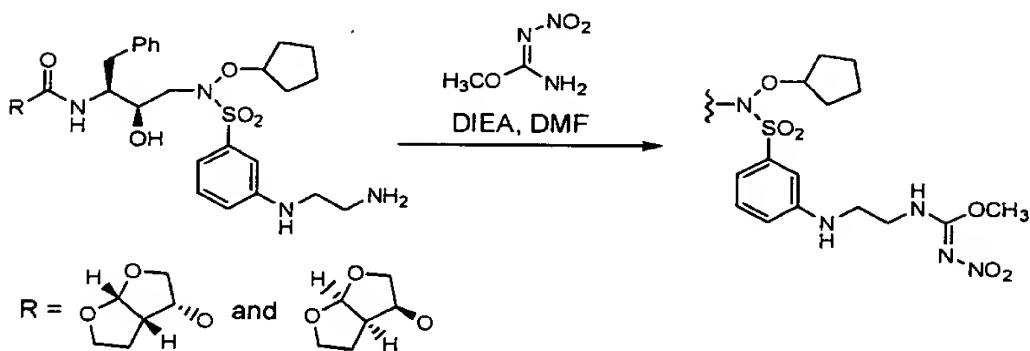
10 1,3-Dioxan-5-yl-N-((1S,2R)-1-benzyl-3-(cyclopentyloxy)(2-  
[(methylsulfonyl)amino]benzimidazol-5-ylsulfonyl)amino-2-  
hydroxypropyl)carbamate. 1,3-Dioxan-5-yl-N-((1S,2R)-1-  
benzyl-3-(cyclopentyloxy)amino-2-hydroxypropyl)carbamate  
(Step 1, Example 55), (0.148 g, 0.4 mmol) was combined with  
15 2-[(methylsulfonyl)amino]benzimidazol-5-ylsulfonyl chloride  
(0.162 g, 0.5 mmol) in anhydrous DMF (4 ml) under a N<sub>2</sub>  
atmosphere. The resulting solution was chilled to 0°C and  
diisopropylethylethyl amine (0.196 ml, 1.1 mmol) was added.  
The reaction was allowed to warm to room temperature and  
20 stirred for 24 hours. Reaction mixture was diluted in EtOAc  
and washed with sat. NaHCO<sub>3</sub>, 0.5N KHSO<sub>4</sub> and brine. Organic  
phase was dried with MgSO<sub>4</sub> and solvent was removed in vacuo.  
Purification by flash chromatography (EtOAc to 2% MeOH/EtOAc  
to 4%). Recovered 0.159 g (64%) of the product as a white  
25 foam. Rf= 0.48 (5% MeOH/EtOAc). <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.10  
(1H, s), 7.67 (1H, d), 7.41 (1H, d), 7.30-7.15 (5H, m), 6.35  
(2H, s), 5.14 (1H, d), 4.90 (1H, d), 4.85 (1H, m), 4.72 (1H, d),

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4.48 (1H, m), 3.93-3.73 (5H, m), 3.29 (3H, s), 1.89-1.70 (4H, m), 1.69-1.47 (4H, m). LRMS (M+H)<sup>+</sup> 668.0.

Example 133

5



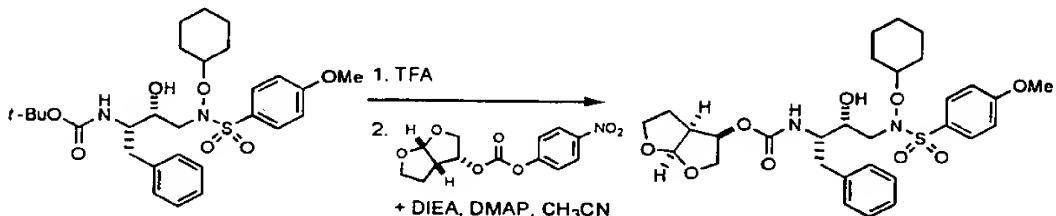
*N*-[2-(3-[(2*R*,3*S*)-3-[(3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl]oxy]carbonylamino)-2-hydroxy-4-phenylbutyl](cyclopentyloxy)amino]sulfonylanilinoethyl]-*O*-methyl-*N*'-(nitro)isourea and *N*-[2-(3-[(2*R*,3*S*)-3-[(3*S*,3*aR*,6*aS*)hexahydrofuro[2,3-*b*]furan-3-yl]oxy]carbonylamino)-2-hydroxy-4-phenylbutyl](cyclopentyloxy)amino]sulfonylanilinoethyl]-*O*-methyl-*N*'-(nitro)isourea. A solution of 25 mg (0.040 mmol) of a 1:1 mixture of (3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(3-[(2-aminoethyl)amino]phenylsulfonyl)(cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate and (3*S*,3*aR*,6*aS*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(3-[(2-aminoethyl)amino]phenylsulfonyl)(cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate (Example 83) and 0.008 mL (0.048 mmol) of *N,N*-diisopropyl ethylamine in 1.5 mL of anhydrous DMF was treated with 6 mg (0.05 mmol) of *O*-methyl-*N*-nitroisourea (Heyboer et al. Rec. Chim Trav. Pay-Bas (1962), 81, 69-72). The resulting solution was stirred at RT. After

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20 hours the solution was concentrated *in vacuo* and the residue subjected to flash chromatography (silica gel, 85:15 CH<sub>2</sub>Cl<sub>2</sub>/2M NH<sub>3</sub> in MeOH) to afford 21 mg (72%) of the desired product as a white foam. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.60-7.06 (12H), 5 5.63-4.65 (4H), 4.10-2.50 (18H), 1.90-1.31 (10H). LCMS (ESI): 721 (M+H).

Example 134

10



(3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-

benzyl-3-(cyclohexyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-

15 hydroxypropyl)carbamate. *tert*-butyl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclohexyloxy)[(4-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate (0.09 mmol, 50 mg) was stirred in 1 mL trifluoroacetic acid (TFA) at room temperature for 5 hours. The TFA was removed under vacuum, and the resulting residue was dissolved in ethyl acetate, washed with 5% aq. potassium carbonate solution, brine, dried over magnesium sulfate, and concentrated to a residue. The resulting free amine, (2*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-2-yl 4-

20 nitrophenyl carbonate (0.09 mmol, 27 mg),

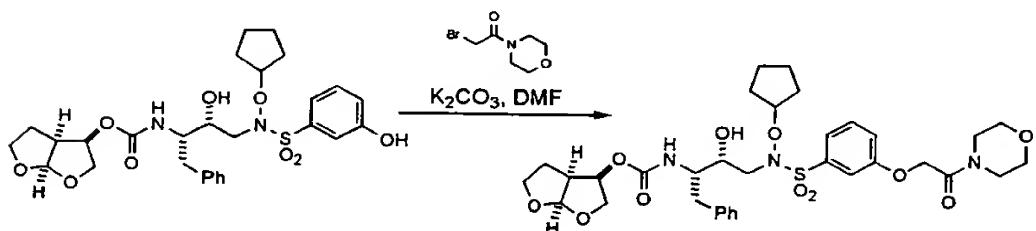
25 diisopropylethylamine (0.13 mmol, 0.018 mL), a crystal of *N,N*-dimethylaminopyridine, 4 Å molecular sieves and acetonitrile (0.5 mL) were combined and stirred at room temperature for 3 days. The reaction solution was concentrated to a residue, dissolved in ethyl acetate, 30 washed with 1N HCl, 5% aq. potassium carbonate solution, brine, dried over magnesium sulfate, and concentrated under

- 252 -

vacuum. The crude residue was purified by crystallization from ether to yield 15 mg (27%) of white crystals.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.71 (2H, d), 7.28-7.16 (6H, m), 6.97 (2H, d), 5.63-5.61 (1H, m), 5.00-4.98 (1H, m), 4.87-4.77 (1H, m), 4.24-5 4.11 (1H, m), 3.98-3.79 (4H, m), 3.87 (3H, s), 3.72-3.61 (2H, m), 3.05 (1H, bs), 3.05-2.72 (6H, m), 2.10-1.98 (2H, m), 1.78-1.68 (2H, m), 1.37-1.04 (6H, m);  $\text{MS}$  (ESI):  $M+H=605$ .

Example 135

10



(3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-15  
benzyl-3-((cyclopentyloxy)[3-(2-morpholino-2-

benzyl-3-((cyclopentyloxy)[3-(2-morpholino-2-

15 15)oxoethoxy)phenyl]sulfonylamino)-2-hydroxypropyl]carbamate. (3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-  
benzyl-3-((cyclopentyloxy)[3-(2-morpholino-2-

15 15)oxoethoxy)phenyl]sulfonylamino)-2-hydroxypropyl]carbamate (0.09 mmol, 50 mg) was combined with 2-bromo-1-morpholino-1-ethanone (0.09 mmol, 18 mg) and  
20 potassium carbonate (0.26 mmol, 36 mg), and stirred in  
anhydrous DMF (1 mL) under nitrogen for 15 hours at room  
temperature. The reaction was concentrated to a residue,  
dissolved in ethyl acetate, washed in distilled water and  
brine, and dried over magnesium sulfate. The dried solution

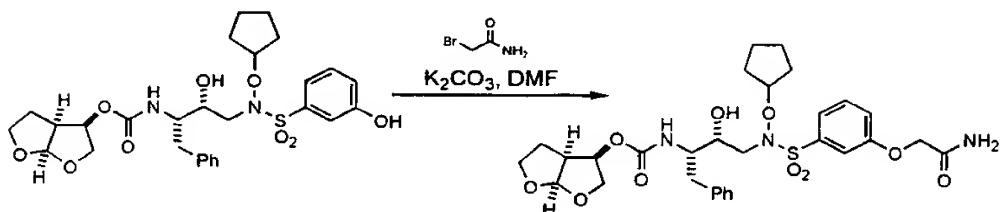
20 20 was then concentrated and purified by silica gel flash  
chromatography (1:1 hexanes/ethyl acetate) to provide 41 mg  
(67%) of a white solid.  $R_f$  = 0.1 (1:1 hexanes/ethyl  
acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.47 (2H, m), 7.38 (1H, m), 7.32-  
7.14 (7H, m), 5.64 (1H, s), 5.03 (2H, m), 4.91-4.76 (1H, m),

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4.78 (2H, s), 3.98-3.89 (2H, m), 3.89-3.77 (2H, m), 3.74-3.63 (8H, m), 3.63-3.52 (2H, m), 3.15 (1H, br.s), 3.08-2.98 (2H, m), 2.98-2.84 (3H, m), 2.84-2.74 (1H, m), 1.89-1.71 (4H, m), 1.71-1.49 (4H, m). MS (ESI): M+H=704.

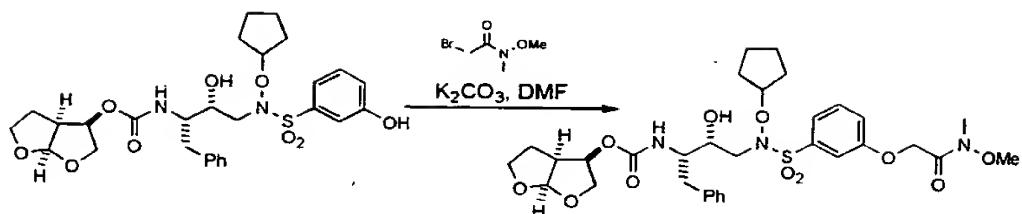
5

Example 136



10 (3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-3-[(3-(2-amino-2-oxoethoxy)phenyl)sulfonyl(cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate. This reaction was set-up, run and purified under the same conditions as for (3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-((cyclopentyloxy)[3-(2-morpholino-2-oxoethoxy)phenyl]sulfonylamino)-2-hydroxypropyl carbamate and generated 44 mg (80%) of a white solid. R<sub>f</sub> = 0.1 (1:1 hexanes/ethyl acetate); H1-NMR (CDCl<sub>3</sub>): δ 7.58-7.42 (2H, m), 7.33-7.06 (8H, m), 6.39 (1H, s), 5.79 (1H, s), 5.63 (1H, s), 5.20-5.12 (1H, m), 5.09-4.99 (1H, m), 4.85 (1H, m), 4.60 (2H, s), 4.0-3.78 (4H, m), 3.71 (2H, m), 3.14 (1H, br.s), 3.09-2.70 (6H, m), 1.93-1.70 (4H, m), 1.70-1.51 (4H, m). MS (ESI): M+H=634.

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Example 137

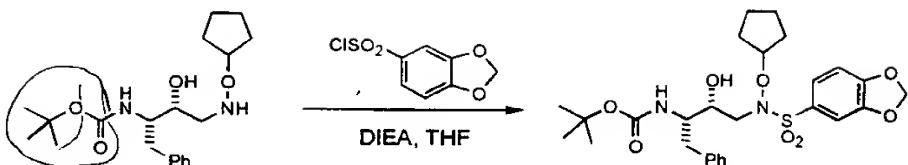
(3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(3-2-[methoxy(methyl)amino]-2-oxoethoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate.

(3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(3-hydroxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate (0.17 mmol, 100 mg), 2-bromo-*N*-methoxy-*N*-methylacetamide (0.26 mmol, 43 mg) and excess potassium carbonate were stirred in anhydrous DMF (1 mL) under nitrogen for 20 hours at room temperature. The DMF was removed under vacuum and the residue was dissolved in ethyl acetate. The crude solution was washed with 1N HCl, saturated aqueous sodium bicarbonate and brine, and dried over magnesium sulfate. The dried solution was concentrated to an oil and purified by silica gel flash chromatography (1:1 hexanes/ethyl acetate) to yield 65 mg (55%) of a white solid.  $R_f$  = 0.1 (1:1 hexanes/ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.45 (2H, m), 7.26 (5H, m), 7.20 (3H, m), 5.64 (1H, s), 5.09-4.97 (2H, m), 4.91 (2H, s), 4.83 (1H, m), 3.92 (2H, m), 3.78 (3H, s), 3.85-3.74 (2H, m), 3.73-3.59 (2H, m), 3.23 (3H, s), 3.28-3.11 (1H, br.s), 3.06-2.84 (5H, m), 2.75 (1H, m), 1.89-1.72 (4H, m), 1.71-1.48 (4H, m).  $\text{MS}$  (ESI):  $M+H=678$ .

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Example 138

Step 1:



5    **tert-butyl N-(1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl) (cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate.** tert-butyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)amino]-2-hydroxypropylcarbamate (0.19 mmol, 69 mg) was combined with 1,3-benzodioxole-5-sulfonyl chloride (0.23 mmol, 50 mg) and diisopropylethylamine (0.57 mmol, 73 mg) in anhydrous THF (2 mL). The reaction stirred under nitrogen for 72 hours at room temperature. The reaction was diluted with diethyl ether, washed with 1 N HCl, saturated aqueous sodium bicarbonate, brine, and was dried over magnesium sulfate. The crude product was concentrated to an oil and purified by silica gel flash chromatography (5:1 hexanes/ethyl acetate) to provide 82 mg (79%) of a white solid. The 1,3-benzodioxole-5-sulfonyl chloride was synthesized as described in Eur. Pat. Appl. 583960, 23 Feb 1994.  $R_f$  = 0.40 (2:1 hexanes/ethyl acetate); H1-NMR ( $CDCl_3$ ):  $\delta$  7.37-7.15 (8H, m), 6.89 (1H, d), 6.10 (2H, s), 4.82 (1H, m), 4.60 (1H, m), 3.82 (2H, m), 3.06 (1H, br.s), 2.94 (2H, m), 2.86 (1H, m), 1.90-1.70 (4H, m), 1.65-1.48 (4H, m), 1.35 (9H, s). MS (ESI):  $M+H=549$ .

10

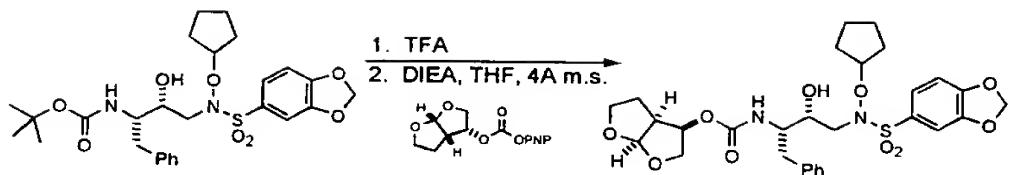
15

20

25

Step 2:

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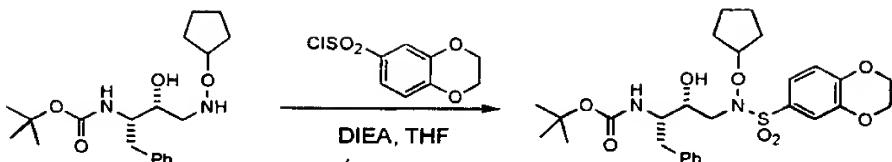
*(3R,3aS,6aR) hexahydrofuro[2,3-*b*]furan-3-yl N-(1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate.* *tert*-butyl *N*-(1*S*,2*R*)-3-

5 [(1,3-benzodioxol-5-ylsulfonyl)(cyclopentyloxy)amino]-1-  
benzyl-2-hydroxypropylcarbamate (0.15 mmol, 80 mg) was  
dissolved in neat trifluoroacetic acid (TFA) and stirred for  
2 hours at room temperature. The TFA was removed under  
vacuum, and the reaction residue was dissolved in ethyl  
acetate. The reaction solution was washed with 5% aqueous  
potassium carbonate, brine and dried over magnesium sulfate.  
The crude solution was concentrated and re-dissolved in 1:1  
hexanes/methylene chloride to exchange out the ethyl  
acetate. The resulting oil was combined with  
15 (2*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-2-yl 4-nitrophenyl  
carbonate (0.22 mmol, 65 mg), diisopropylethylamine (0.44  
mmol, 0.076 mL), 4 Åmolecular sieves and stirred in  
anhydrous THF (2 mL) under nitrogen for 15 hours at room  
temperature. The reaction was diluted with ethyl acetate,  
20 washed with 1N HCl, saturated aqueous sodium bicarbonate,  
brine and was dried over magnesium sulfate. The crude  
product was purified by silica gel flash chromatography (2:1  
hexanes/ethyl acetate) to provide 41 mg (47%) of a white  
solid.  $R_f$  = 0.20 (1:1 hexanes/ethyl acetate);  $^1\text{H-NMR}$   
25 ( $\text{CDCl}_3$ ):  $\delta$  7.41-7.14 (8H, m), 6.91 (1H, d), 6.12 (2H, s), 5.66  
(1H, s), 5.03 (2H, m), 4.84 (2H, m), 3.91 (4H, m), 3.70 (2H, m),  
3.12 (1H, s), 3.01 (2H, m), 2.93 (1H, m), 2.84 (2H, m), 1.91-  
1.71 (4H, m), 1.71-1.49 (4H, m).  $\text{MS (ESI): M+H=606.}$

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Example 139

Step 1:

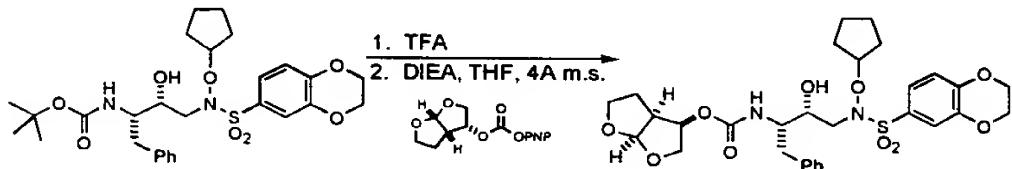


**tert-butyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)(2,3-**

5 **dihydro-1,4-benzodioxin-6-ylsulfonyl)amino]-2-**  
**hydroxypropylcarbamate.** This reaction was set-up, run and  
 purified using the same protocol described for **tert-butyl N-**  
 (1S,2R)-3-[(1,3-benzodioxol-5-  
 ylsulfonyl) (cyclopentyloxy)amino]-1-benzyl-2-  
 10 **hydroxypropylcarbamate.** The 1,4-benzodioxan-6-sulfonyl  
 chloride was synthesized according to the procedure  
 described in Eur. Pat. Appl. 583960, 23 Feb 1994.  $R_f = 0.40$   
 (2:1 hexanes/ethyl acetate); H1-NMR ( $CDCl_3$ ):  $\delta$  7.36-7.18  
 (8H, m), 6.95 (1H, d), 4.82 (1H, m), 4.60 (1H, m), 4.32 (4H, m),  
 15 3.82 (2H, m), 3.05 (1H, br.s), 2.93 (2H, m), 2.87 (1H, m),  
 1.88-1.69 (4H, m), 1.69-1.47 (4H, m), 1.35 (9H, s). MS (ESI):  
 M+H=563.

Step 2:

20



**(3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl N-(1S,2R)-1-**  
**benzyl-3-[(cyclopentyloxy)(2,3-dihydro-1,4-benzodioxin-6-**  
**ylsulfonyl)amino]-2-hydroxypropylcarbamate.** This reaction

25 was set-up, run and purified using the same protocol  
 described for **(3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl N-**  
 (1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)

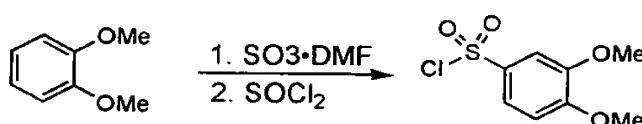
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(cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate.  $R_f$  = 0.20 (1:1 hexanes/ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.37-7.12 (8H, m), 6.97 (1H, d), 5.65 (1H, s), 5.03 (2H, m), 5.06-4.77 (2H, m), 4.81 (1H, m), 4.33 (4H, d), 3.91 (4H, m), 3.70 (2H, m), 3.12 (1H, s), 3.07-2.97 (2H, m), 2.93 (2H, m), 2.85 (2H, m), 1.90-1.70 (4H, m), 1.7-1.46 (4H, m).  $\text{MS}$  (ESI):  $M+H=619$ .

10

Example 140

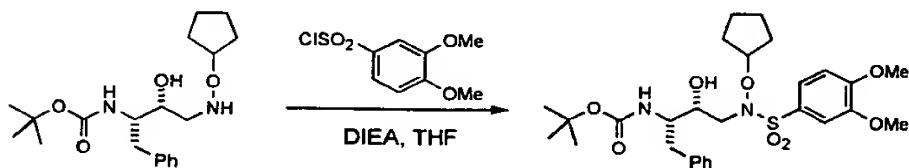
Step 1:



15 **3,4-dimethoxybenzenesulfonyl chloride.** 3,4-dimethoxybenzenesulfonyl chloride was synthesized as described in Eur. Pat. Appl. 583960, 23 Feb 1994.  $R_f = 0.4$  (2:1 hexanes/ethyl acetate).  $^1\text{H-NMR}$ :  $\delta$  7.69 (1H, d), 7.45 (1H, m), 7.00 (1H, d), 4.00 (3H, s), 3.98 (3H, s).

20

Step 2:

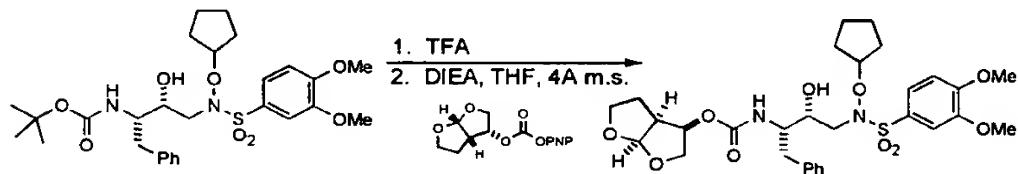


25 **tert-butyl N-((1S,2R)-1-benzyl-3-(cyclopentyloxy)[(3,4-dimethoxyphenyl)sulfonyl]amino)-2-hydroxypropylcarbamate.** *tert-butyl N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)amino]-2-hydroxypropylcarbamate* (0.41 mmol, 150 mg) was combined with 3,4-dimethoxybenzenesulfonyl chloride (0.82 mmol, 142 mg) and diisopropyl-ethylamine (2.05 mmol, 0.358 mL) in anhydrous THF (1 mL). The reaction was allowed to reflux

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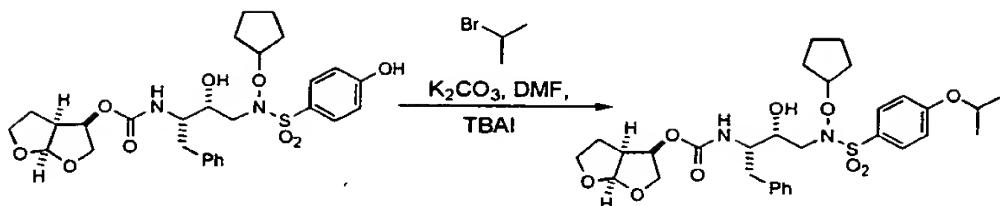
for 72 hours. The reaction was worked-up by diluting with an equal volume of ethyl acetate, washing with 1N HCl, saturated aq. sodium bicarbonate and brine, and dried over magnesium sulfate. The crude solution was concentrated to 5 an oil and purified by silica gel chromatography (2:1 hexanes/ethyl acetate) yielding 100 mg (43%) of a white solid.  $R_f$  = 0.1 (1:1 hexanes/ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.41 (1H, d), 7.33-7.17 (7H, m), 6.95 (1H, d), 4.82 (1H, m), 4.52 (1H, m), 3.96 (3H, s), 3.93 (3H, s), 3.80 (2H, m), 10 3.08 (1H, br.s), 3.00-2.79 (3H, m), 1.90-1.45 (8H, m), 1.32 (9H, s).

## Step 3:



15  $(3R,3aS,6aR)$  hexahydrofuro[2,3-b]furan-3-yl  $N$ -((1S,2R)-1-benzyl-3-(cyclopentyloxy)[(3,4-dimethoxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate. This reaction was set-up, run and purified using the same protocol described for 20  $(3R,3aS,6aR)$  hexahydrofuro[2,3-b]furan-3-yl  $N$ -(1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl) (cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate.  $R_f$  = 0.20 (2:1 hexanes/ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.42 (1H, d), 7.35-7.14 (8H, m), 6.97 (1H, d), 5.64 (1H, s), 5.00 (1H, m), 4.80 (2H, m), 3.96 (3H, s), 3.93 (3H, s), 3.99-3.80 (4H, m), 3.67 (2H, m), 3.15 (1H, br.s), 3.08-2.98 (2H, m), 2.95-2.75 (3H, m), 1.90-1.71 (4H, m), 1.70-1.43 (4H, m). MS (ESI):  $M+H=621$ .

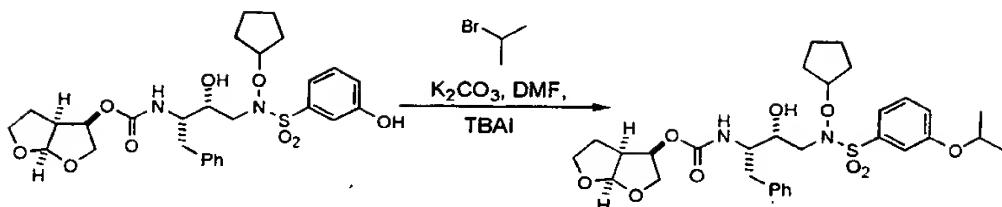
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Example 141

(3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-

5      *benzyl-3-(cyclopentyloxy)[(4-*  
*isopropoxypyhenyl)sulfonyl]amino-2-hydroxypropyl)carbamate.*

(3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-  
*benzyl-3-(cyclopentyloxy)[(4-hydroxyphenyl)sulfonyl]amino-2-*  
*hydroxypropyl)carbamate* (0.13 mmol, 75 mg) was combined with  
10      2-bromopropane (0.26 mmol, 0.025 mL), potassium carbonate  
*(0.65 mmol, 90 mg), tetrabutylammonium iodide (5 mg) and*  
*anhydrous DMF (1 mL). The reaction stirred under a nitrogen*  
*atmosphere at room temperature for 15 hours, then was heated*  
15      to 50°C for 3 hours. The reaction mixture was concentrated  
*under vacuum to a residue and diluted with ethyl acetate (2*  
*mL). The reaction was washed in distilled water and brine,*  
*and was dried over magnesium sulfate. The dried solution*  
*was then concentrated to an oil and purified by silica gel*  
*chromatography (2:1 hexanes/ethyl acetate) to yield 61 mg*  
20      (76 %) of a white solid.  $R_f$  = 0.50 (2:1 hexanes/ethyl  
*acetate); H1-NMR (CDCl3):  $\delta$  7.69 (2H,d), 7.33-7.13 (6H,m),*  
*6.96 (2H,d), 5.65 (1H,s), 5.02 (1H,m), 4.86 (1H,m), 4.80*  
*(1H,m), 4.65 (1H,m), 3.99-3.80 (5H,m), 3.69 (2H,m), 3.11*  
*(1H,br.s), 3.09-2.98 (3H,m), 2.91 (1H,m), 2.83 (1H,m), 1.89-*  
25      1.72 (4H,m), 1.7-1.46 (4H,m), 1.38 (6H,d). MS (ESI):  
*M+H=619.*

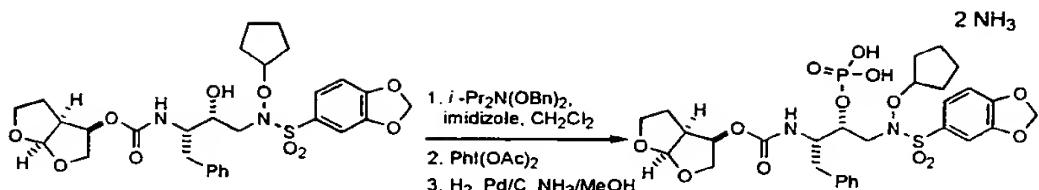
Example 142

(3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-

5      **benzyl-3-(cyclopentyloxy)[(3-isopropoxypyphenyl)sulfonyl]amino-2-hydroxypropyl carbamate.** (3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(3-hydroxyphenyl)sulfonyl]amino-2-hydroxypropyl carbamate (0.13 mmol, 75 mg) was combined with 2-bromopropane (0.26 mmol, 0.025 mL), potassium carbonate (0.65 mmol, 90 mg), tetrabutylammonium iodide (5 mg) and anhydrous DMF (1 mL). The reaction was stirred under a nitrogen atmosphere at room temperature for 72 hours. The reaction mixture was concentrated under vacuum to a residue and diluted with 10      ethyl acetate (2 mL). The reaction was washed in distilled water and brine, and was dried over magnesium sulfate. The dried solution was then concentrated to an oil and purified by silica gel chromatography (2:1 hexanes/ethyl acetate) to yield 38 mg (48 %) of a white solid.  $R_f$  = 0.40 (2:1

15      hexanes/ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.40 (1H, m), 7.33-7.10 (9H, m), 5.63 (1H, s), 5.00 (1H, m), 4.80 (2H, m), 4.58 (1H, m), 3.88 (4H, m), 3.67 (2H, m), 3.13 (1H, br. s), 3.00 (2H, m), 2.94-2.74 (2H, m), 1.88-1.71 (5H, m), 1.69-1.43 (5H, m), 1.35 (6H, d).

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Example 143

(3*R*, 3*aS*, 6*aR*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*, 2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(cyclopentyloxy)amino]-1-benzyl-2-(phosphonoxy)propyl]carbamate.

## Step 1:

(3*R*, 3*aS*, 6*aR*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*, 2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate (0.38 mmol, 231 mg) was combined with dibenzyl diisopropylphosphoramidite (0.57 mmol, 0.192 mL), imidazole (0.38 mmol, 27 mg) and methylene chloride (5 mL), and stirred for 15 hours at room temperature. The reaction was concentrated to a residue and purified by silica gel chromatography (2:1 hexanes/ethyl acetate) which produced 325 mg of a clear oil.

## Step 2:

The oil from the previous step was oxidized by combining with iodobenzene diacetate (0.57 mmol, 185 mg) and acetonitrile (10 mL). The reaction was instantaneous and was concentrated to a crude white solid. The product was purified by silica gel chromatography (1:1 hexanes/ethyl acetate) and produced 170 mg of a sticky white residue.

## Step 3:

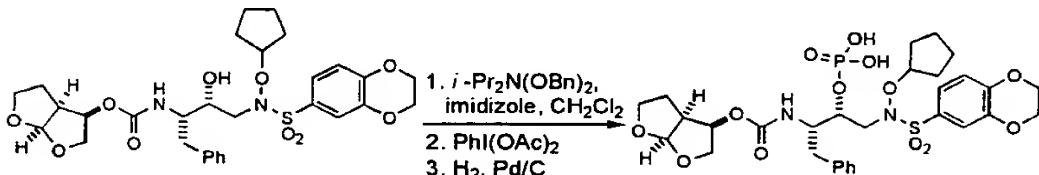
The phosphate ester from the previous step was stirred vigorously with 10% Pd/Carbon (34 mg) and methanolic ammonia (2 M in methanol, 2 mL) under a hydrogen atmosphere for 3 hours at room temperature. The reaction was filtered, and the filtrate was concentrated to a residue and crystallized.

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from methylene chloride/diethyl ether. The reaction produced 80 mg (31% - 3 steps) of white crystals.  $R_f = 0.20$  (1:1 hexanes/ethyl acetate); H1-NMR ( $D_2O$ ):  $\delta$  7.38 (1H, m), 7.26-7.05 (6H, m), 6.95 (1H, m), 6.00 (2H, d), 5.51-5.42 (1H, m), 4.78 (1H, m), 4.30 (1H, m), 4.16-3.99 (1H, m), 3.86-3.62 (3H, m), 3.57-3.42 (1H, m), 3.41-3.27 (1H, m), 3.07-2.90 (2H, m), 2.89-2.72 (1H, m), 2.55-2.43 (1H, m), 1.82-1.57 (5H, m), 1.57-1.30 (5H, m), 1.00-0.90 (1H, m). MS (ESI):  $M+H=685$ .

10

Example 144



(3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-benzyl-3-[(cyclopentyloxy)(2,3-dihydro-1,4-benzodioxin-6-ylsulfonyl)amino]-2-(phosphonooxy)propyl]carbamate

Step 1:

(3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-[(cyclopentyloxy)(2,3-dihydro-1,4-benzodioxin-6-ylsulfonyl)amino]-2-hydroxypropylcarbamate (0.14 mmol, 86 mg) was combined with dibenzyl diisopropylphosphoramidite (0.21 mmol, 0.070 mL), imidazole (0.18 mmol, 13 mg) and methylene chloride (3 mL), and stirred for 20 hours at room temperature. The reaction was concentrated to a residue and purified by silica gel chromatography (2:1 hexanes/ethyl acetate) which produced 100 mg of a clear oil.

Step 2:

The oil from the previous step was oxidized by combining with iodobenzene diacetate (0.18 mmol, 56 mg) and

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acetonitrile (3 mL). The reaction was instantaneous and was concentrated to a crude white solid. The product was purified by silica gel chromatography (1:1 hexanes/ethyl acetate) and produced 65 mg of a white foam.

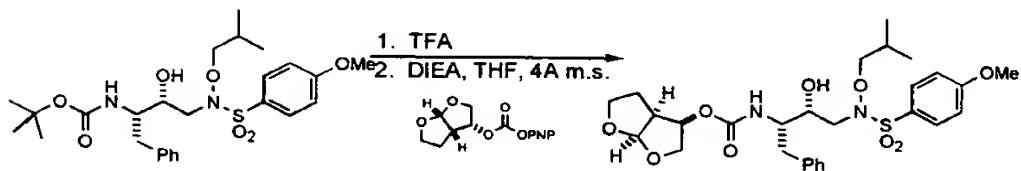
5

**Step 3:**

The phosphate ester from the previous step was stirred vigorously with 10% Pd/Carbon (12 mg) and methanolic ammonia (2 M in methanol, 2 mL) under a hydrogen atmosphere for 2

10 hours at room temperature. The reaction was filtered, and the filtrate was concentrated to a residue and crystallized from methylene chloride/diethyl ether. The crystals were purified by RP HPLC (acetonitrile/water) and produced 20 mg (20% - 3 steps) of a white solid after lyophylization.  $R_f$  = 15 0.20 (1:1 hexanes/ethyl acetate);  $^1\text{H-NMR}$  ( $\text{D}_2\text{O}$ ):  $\delta$  7.31 (1H, m), 7.26-7.07 (6H, m), 7.03-6.97 (1H, m), 5.52-5.43 (1H, m), 4.78 (1H, m), 4.34-4.15 (5H, m), 4.15-4.00 (1H, m), 3.79-3.65 (3H, m), 3.53-3.41 (1H, m), 3.38-3.23 (1H, m), 3.08-2.92 (2H, m), 2.89-2.71 (1H, m), 2.52-2.43 (1H, m), 1.80-1.57 (5H, m), 1.56-1.33 (5H, m), 0.98 - 0.88 (1H, m). MS (ESI): 20  $M+\text{H}=699$ .

**Example 145**



25

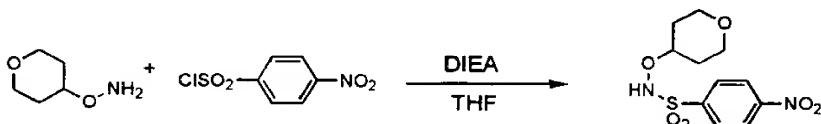
(3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-benzyl-2-hydroxy-3-isobutoxy[(4-methoxyphenyl)sulfonyl]aminopropyl)carbamate. This reaction was set-up, run and purified using the same protocol 30 described for (3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-

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(1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)  
(cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate.  $R_f$   
= 0.20 (1:1 hexanes/ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.74  
(2H, d), 7.35-7.12 (6H, m), 7.01 (2H, d), 5.65 (1H, s), 5.03  
5 (1H, m), 4.89 (1H, m), 3.90 (3H, s), 4.03-3.79 (7H, m), 3.70  
(2H, m), 3.11 (1H, br, s), 3.04-2.69 (5H, m), 1.86 (1H, m), 0.92  
(6H, m).  $\text{MS}$  (ESI):  $M+\text{Na}=601$ .

Example 146

10 Step 1:

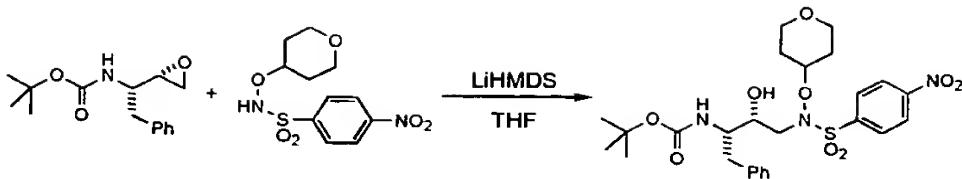


4-nitro-*N*-(tetrahydro-2*H*-pyran-4-yl)benzenesulfonamide  
4-tetrahydropyranoxyhydroxylamine (33.2 mmol, 3.77g) and 4-

15 nitrobenzenesulfonylchloride (38.6 mmol, 8.56 g) were  
combined in anhydrous THF (100 mL) with  
diisopropylethylamine (69.3 mmol, 11.2 mL). The reaction  
was stirred at room temperature for 48 hours. Hydrazine (2  
mL) was injected to the stirring solution to break-up the  
20 bisarylsulfonamide dimer biproduct. The reaction was  
stirred for an additional 24 hours. The reaction was  
diluted in ethyl acetate, washed in brine, filtered to  
remove insoluble solids and concentrated. The crude was  
purified by crystallization from hot ethyl acetate to  
25 provide 3.5 g (36%) of white crystals.  $R_f$  = 0.3 (2:1  
hexanes/ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.42 (2H, d), 8.13  
(2H, d), 6.93 (1H, s), 4.27 (1H, m), 3.91 (2H, m), 3.45 (2H, m),  
2.02 (2H, m), 1.61 (2H, m).

30 Step 2:

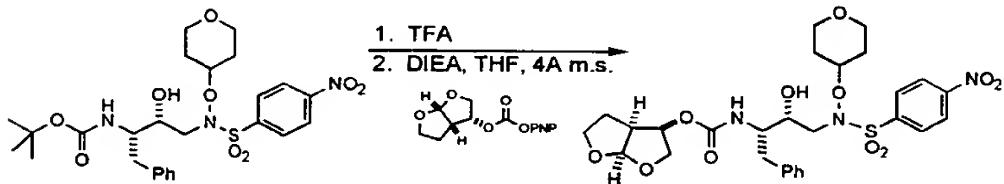
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*tert*-butyl (1*S*,2*R*)-1-benzyl-2-hydroxy-3-[(4-nitrophenyl)sulfonyl](tetrahydro-2*H*-pyran-4-yloxy)amino]propylcarbamate. 4-nitro-*N*-(tetrahydro-2*H*-pyran-4-yloxy)benzenesulfonamide (8.6 mmol, 2.61 g)

5 was combined with *tert*-butyl *N*-(1*S*)-1-[(2*S*)oxiran-2-yl]-2-phenylethylcarbamate (7.2 mmol, 1.89 g), lithium bis(trimethylsilyl) amide (1.0 M in THF) (1.4 mmol, 1.4 mL) and anhydrous THF (80 mL). The reaction was stirred under 10 nitrogen at room temperature for 96 hours. The reaction was diluted in ethyl acetate (200 mL) and washed with a 5% aqueous solution of potassium carbonate, brine, and was 15 dried over magnesium sulfate. The crude solution was concentrated to a foam and purified by crystallization from diethylether to provide 3.5 g (86%) of light yellow 20 crystals.  $R_f$  = 0.3 (2:1 hexanes/ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.36 (2H, d), 7.96 (2H, d), 7.33-7.15 (6H, m), 4.55 (1H, m), 4.42 (1H, m), 3.95 (2H, m), 3.77 (2H, m), 3.43 (2H, m), 3.07 (1H, br.s), 2.90 (2H, m), 2.03 (2H, m), 1.65-1.42 (3H, m), 1.32 (9H, s).

### Step 3:



(3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-benzyl-

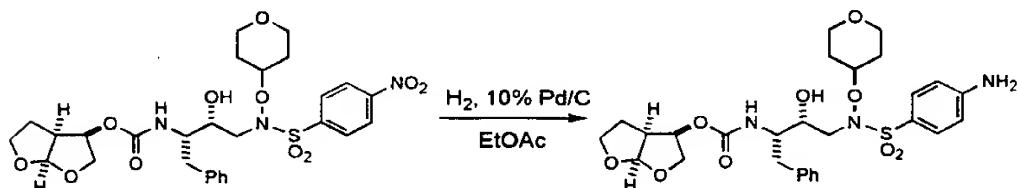
25 2-hydroxy-3-[(4-nitrophenyl)sulfonyl](tetrahydro-2*H*-pyran-4-yloxy)amino]propylcarbamate. This reaction was set-up,

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run and purified using the same protocol described for (3*R*, 3*aS*, 6*aR*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*, 2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl) (cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate.  $R_f$  = 0.1 (1:1 hexanes/ethyl acetate);  $^1$ H-NMR ( $CDCl_3$ ):  $\delta$  8.38 (2H, d), 7.95 (2H, d), 7.33-7.20 (4H, m), 7.17 (2H, m), 5.64 (1H, s), 5.02 (1H, m), 4.87 (1H, m), 4.45 (1H, m), 4.00-3.77 (6H, m), 3.68 (2H, m), 3.43 (2H, m), 3.31-2.30 (4H, m), 2.05 (2H, m), 1.86 (1H, m), 1.76-1.42 (4H, m).

10

## Step 4:



(3*R*, 3*aS*, 6*aR*) hexahydrofuro[2,3-*b*]furan-3-[(4-

15 aminophenyl)sulfonyl](tetrahydro-2*H*-pyran-4-yloxy)amino]-1-benzyl-2-hydroxypropylcarbamate. (3*R*, 3*aS*, 6*aR*) hexahydrofuro[2,3-*b*]furan-3-yl (1*S*, 2*R*)-1-benzyl-2-hydroxy-3-[(4-nitrophenyl)sulfonyl](tetrahydro-2*H*-pyran-4-yloxy)amino]propylcarbamate (0.16 mmol, 100 mg) was combined with 10% palladium on carbon (20 mg) and ethyl acetate (2 mL), and the reaction was stirred vigorously under a hydrogen atmosphere for 15 hours. The reaction was filtered and the filtrate was concentrated to an oil. The crude product was purified by crystallization from hexanes/ethyl acetate to provide 30 mg (32%) of fine white crystals.  $R_f$  = 0.5 (ethyl acetate);  $^1$ H-NMR ( $CDCl_3$ ):  $\delta$  7.56 (2H, d), 7.33-7.11 (6H, m), 6.72 (2H, d), 5.64 (1H, s), 5.0 (1H, m), 4.83 (1H, m), 4.39 (1H, septet), 4.01-3.78 (6H, m), 3.73-3.59

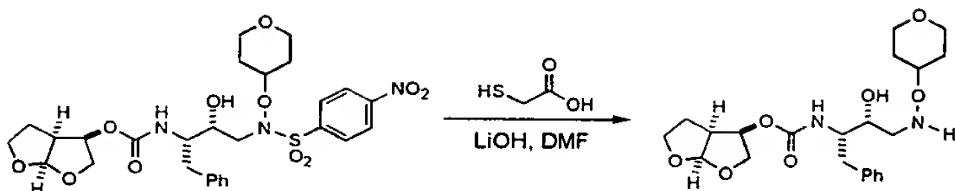
- 268 -

(2H, m), 3.48-3.33 (2H, m), 3.31-2.28 (2H, br.s), 3.16-2.72 (6H, m), 1.74-1.45 (5H, m). MS (ESI): M+H=592.

Example 147

5

Step 1:

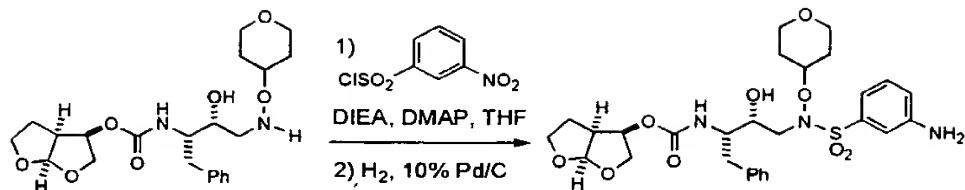


(3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-benzyl-2-hydroxy-3-[(4-nitrophenyl)sulfonyl]propylcarbamate. (3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-benzyl-2-hydroxy-3-[(4-nitrophenyl)sulfonyl]propylcarbamate (3.62 mmol, 2.25g) was combined with mercaptoacetic acid (7.24 mmol, 0.501 mL), lithium hydroxide (14.5 mmol, 607 mg) and anhydrous DMF (10 mL) and stirred for 2 hours at room temperature under nitrogen. The reaction was concentrated to a red suspension under vacuum and dissolved in 700 mL ethyl acetate. The crude solution was washed with distilled water, saturated aqueous sodium bicarbonate, brine and dried over magnesium sulfate. The crude product was concentrated to a yellow solid and purified by silca gel chromatography (10:1 ethyl acetate/methanol) followed by crystallization from methylene chloride/hexanes to provide 650 mg (41%) of white crystals.  $R_f$  = 0.15 (ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.39-7.18 (6H, m), 5.69 (1H, s), 5.08 (2H, m), 4.25 (1H, m), 4.10-3.58 (8H, m), 3.52-3.27 (3H, m), 3.19 (1H, m), 3.03 (1H, br.s), 2.90 (1H, m), 2.71 (1H, m), 2.13-1.80 (3H, m), 1.74-1.29 (4H, m).

30

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## Step 2:

(3*R*, 3*aS*, 6*aR*) hexahydrofuro[2,3-*b*]furan-3-yl 3-[(3-5 aminophenylsulfonyl](tetrahydro-2*H*-pyran-4-*Y*loxy)amino]-1-  
benzyl-2-hydroxypropylcarbamate.

## Step 1:

(3*R*, 3*aS*, 6*aR*) hexahydrofuro[2,3-*b*]furan-3-yl (1*S*, 2*R*)-1-benzyl-10 2-hydroxy-3-[(tetrahydro-2*H*-pyran-4-  
yloxy)amino]propylcarbamate (0.17 mmol, 75 mg) was combined  
with 3-nitrobenzenesulfonyl chloride (0.26 mmol, 57 mg),  
diisopropylethylamine (0.69 mmol, 0.120 mL), *N,N*-  
dimethylaminopyridine (5 mg), and anhydrous THF (5 mL). The  
15 reaction was stirred at 50°C for 15 hours under nitrogen.  
The reaction product was diluted in ethyl acetate (10 mL),  
washed with 1N HCl, saturated aqueous sodium bicarbonate,  
brine, and was dried over magnesium sulfate. The crude  
solution was concentrated under vacuum and purified by  
20 silica gel chromatography (1:1 methylene chloride/ethyl  
acetate) to provide 100 mg (93%) of a white solid.

## Step 2:

The product of the previous step was combined with 10%

25 palladium on carbon (20 mg) and stirred vigorously in ethyl  
acetate (2 mL) under hydrogen for 20 hours. The reaction  
was filtered and concentrated under vacuum. The crude  
product was purified by crystallization (diethylether/ethyl  
acetate/hexanes) to yield 40 mg (42%) of white crystals.30  $R_f$  = 0.45 (ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.41-7.02

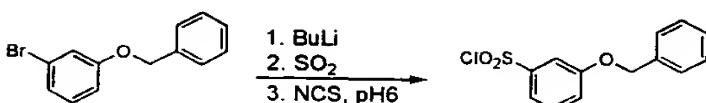
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(10H, m), 6.96 (1H, br.s), 5.62 (1H, s), 5.02 (1H, m), 4.85 (1H, br.s), 4.42 (1H, m), 4.02-3.77 (6H, m), 3.69 (2H, m), 3.48-3.33 (3H, m), 3.22-2.52 (6H, m), 1.87-1.30 (5H, m). MS (ESI): M+H=592.

5

Example 148

Step 1:



**3-benzyloxybenzenesulfonyl chloride**

The aryl bromide (12 g, 45.6 mmol) was dissolved in THF (100 mL) and cooled to -78°C. *n*-Butyl lithium 1.6 M in hexanes

15 (28.5 mL, 45.6 mmol) was injected and the reaction stirred for 1 hr. before being warmed to 0°C. The resulting

solution was then transferred to a -78°C solution of SO<sub>2</sub> (41 mL, 913 mmol), Et<sub>2</sub>O (100 mL) and THF (100 mL). The solution became a yellow suspension immediately upon addition of the

20 aryl lithium. The suspension was warmed to room temperature and stirred for 3 days. The yellow mixture was sparged with nitrogen for 2 hr. The suspension was concentrated and the resulting solid triturated with Et<sub>2</sub>O to provide 7.23 g of

the sulfinate intermediate. The lithium sulfinate was

25 stirred in a bi-phasic mixture of pH 6 aqueous dibasic sodium phosphate buffer (27 g in 200 mL distilled water - adjusted to pH 6 with conc. phosphoric acid) and ethyl acetate (200 mL) and cooled to 0°C. While stirring

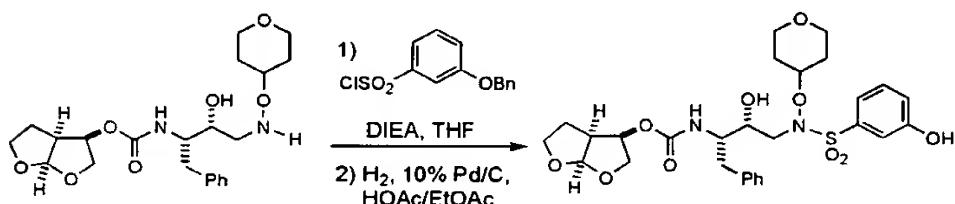
vigorously, *N*-chlorosuccinimide (3.80 g, 28.4 mmol) was

30 added. The reaction was immediately warmed to room temperature and the aqueous layer was drained. The organic layer was washed with distilled water, brine and dried over

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magnesium sulfate. The crude was concentrated to a yellow solid under reduced pressure and washed with Et<sub>2</sub>O. The product was purified by eluting through a silica gel column with Et<sub>2</sub>O and resulted in 4.81 g (37%) of the desired 5 product. R<sub>f</sub> = 0.2 (5:1 hexanes/ethyl acetate). H1-NMR: 7.67-7.27 (9H, m), 5.13 (2H, s).

## Step 2:



10 (3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl 1-benzyl-2-hydroxy-3-[(3-hydroxyphenyl)sulfonyl](tetrahydro-2*H*-pyran-4-yloxy)amino]propylcarbamate.

## Step 1:

15 (3*R*,3a*S*,6a*R*) hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-benzyl-2-hydroxy-3-[(tetrahydro-2*H*-pyran-4-yloxy)amino]propylcarbamate (0.17 mmol, 75 mg) was combined with 3-benzyloxybenzenesulfonyl chloride (0.26 mmol, 73 mg), diisopropylethylamine (0.69 mmol, 0.12 mL) in methylene 20 chloride (2 mL) and allowed to stir for 15 hours at room temperature under nitrogen. The reaction was diluted with ethyl acetate and washed with 1N HCl, 5% aqueous potassium bicarbonate solution, brine and was dried over magnesium sulfate. The solution was concentrated under vacuum and the 25 crude product was purified by silica gel chromatography (1:1 hexanes/ethyl acetate) to provide 60 mg (51%) of a clear oil.

## Step 2:

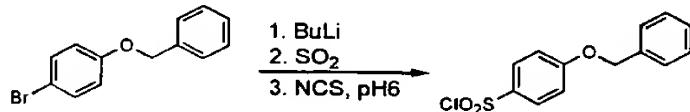
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The product of the previous step was stirred vigorously with 10% palladium on carbon (20 mg), acetic acid (0.5 mL), and ethyl acetate (2mL) under hydrogen for 6 hours. The reaction was filtered and concentrated to an oil. The crude 5 product was purified by silica gel chromatography (1:1 hexanes/ethyl acetate), and crystallized from diethylether/hexanes to provide 31 mg (36%) of white crystals.  $R_f = 0.2$  (1:1 methylene chloride/ethyl acetate); H1-NMR ( $CDCl_3$ ):  $\delta$  7.40 (2H, m), 7.32-7.21 (5H, m), 7.17 10 (3H, m), 6.81 (1H, br.s), 5.69 (1H, s), 5.00 (2H, m), 4.40 (1H, m), 4.02-3.70 (8H, m), 3.48-3.35 (2H, m), 3.23-2.71 (6H, m), 2.04 (2H, m), 1.79-1.67 (1H, m), 1.65-1.42 (3H, m). MS (ESI):  $M+H=593$ .

15

Example 149

Step 1:

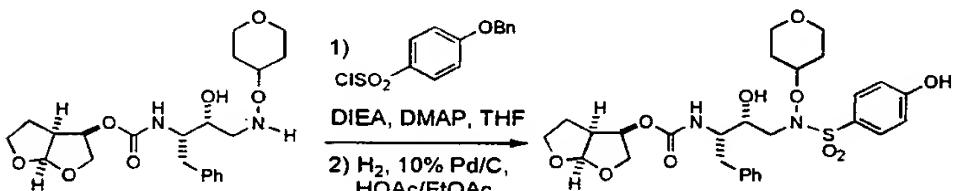


20 **4-benzyloxybenzenesulfonyl chloride.** The aryl bromide (12 g, 45.6 mmol) was dissolved in THF (100 mL) and cooled to -78 °C. *n*-Butyl lithium 1.6 M in hexanes (28.5 mL, 45.6 mmol) was injected and the reaction stirred for 1hr. before being warmed to 0°C. The resulting solution was then 25 transferred to a -78°C solution of  $\text{SO}_2$  (41 mL, 913 mmol),  $\text{Et}_2\text{O}$  (100 mL) and THF (100 mL). The solution became a yellow suspension immediately upon addition of the aryl lithium. The suspension was warmed to room temperature and sparged with nitrogen for 1 hr. The suspension was 30 concentrated to a yellow solid and triturated with  $\text{Et}_2\text{O}$  to provide 6.27 g of the sulfinate intermediate. The lithium sulfinate was stirred in a bi-phasic mixture of pH 6 aqueous

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dibasic sodium phosphate buffer (27 g in 200 mL distilled water - adjusted to pH 6 with conc. phosphoric acid) and ethyl acetate (200 mL) and cooled to 0°C. While stirring vigorously, *N*-chlorosuccinimide (3.27 g, 24.7 mmol) was 5 added. The reaction was immediately warmed to room temperature and the aqueous layer was drained. The organic layer was concentrated to a yellow solid under reduced pressure. The crude sulfonyl chloride was purified by silica gel chromatography (5:1 hexanes/ethyl acetate) to 10 provide 3.35g (26%) of an off-white solid.  $R_f$  = 0.2 (5:1 hexanes/ethyl acetate).  $^1\text{H-NMR}$ :  $\delta$  7.97 (2H, d), 7.45-7.30 (5H, m), 7.10 (2H, d), 5.16 (2H, s).

## Step 2:



15  $(3R,3aS,6aR)$  hexahydrofuro[2,3-*b*]furan-3-yl 1-benzyl-2-hydroxy-3-[(4-hydroxyphenyl)sulfonyl](tetrahydro-2*H*-pyran-4-yloxy)amino]propylcarbamate.

## 20 Step 1:

21  $(3R,3aS,6aR)$  hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-benzyl-2-hydroxy-3-[(tetrahydro-2*H*-pyran-4-yloxy)amino]propylcarbamate (0.17 mmol, 75 mg) was combined with 4-benzyloxybenzenesulfonyl chloride (0.26 mmol, 73 mg), 25 diisopropylethylamine (0.69 mmol, 0.12 mL), and a few crystals of *N,N*-dimethylaminopyridine in a 1:1 solution of anhydrous THF/methylene chloride (2 mL) and allowed to stir for 15 hours at room temperature under nitrogen. The reaction was diluted with ethyl acetate and washed with 1N

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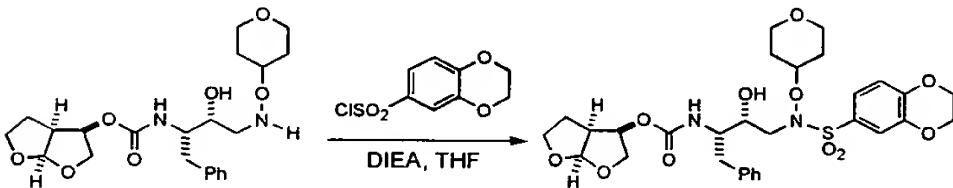
5 HCl, 5% aqueous potassium carbonate solution, brine and was dried over magnesium sulfate. The solution was concentrated under vacuum and the crude product was purified by silica gel chromatography (1:1 hexanes/ethyl acetate) to provide 50 mg (43%) of a clear oil.

Step 2:

10 The product of the previous step was stirred vigorously with 10% palladium on carbon (10 mg), acetic acid (0.5 mL), and ethyl acetate (2 mL) under hydrogen for 15 hours. The reaction was filtered and concentrated to an oil. The crude product was crystallized from diethylether/hexanes to provide 8 mg (19%) of white crystals.  $R_f = 0.2$  (1:1 15 methylene chloride/ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.66 (2H,d), 7.32-7.12 (6H,m), 6.94 (2H,d), 6.25 (1H,br.s), 5.66 (1H,s), 4.98 (1H,m), 4.76 (1H,m), 4.41 (1H,m), 4.00-3.78 (6H,m), 3.68 (2H,m), 3.51-3.36 (2H,m), 3.29-2.51 (6H,m), 2.12-1.95 (2H,m), 1.69 (1H,m), 1.63-1.45 (2H,m). MS (ESI):  $M+H=593$ .

20

Example 150



25  $(3R,3aS,6aR)$ hexahydrofuro[2,3-*b*]furan-3-yl 1-benzyl-3-[(2,3-dihydro-1,4-benzodioxin-6-ylsulfonyl) (tetrahydro-2*H*-pyran-4-yloxy)amino]-2-hydroxypropylcarbamate.

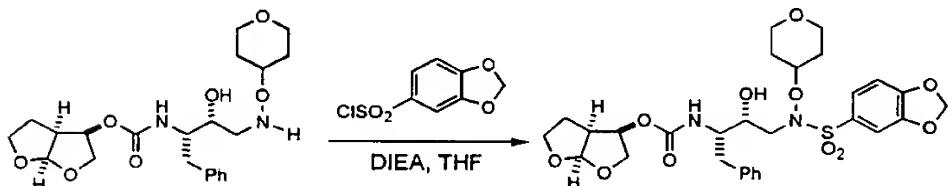
30  $(3R,3aS,6aR)$ hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-benzyl-2-hydroxy-3-[(tetrahydro-2*H*-pyran-4-yloxy)amino]propylcarbamate (0.17 mmol, 75 mg) was combined with 1,4-benzodioxan-6-sulfonyl chloride (0.21 mmol, 48 mg),

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diisopropylethylamine (0.69 mmol, 0.12 mL) in anhydrous THF (2 mL) and allowed to stir for 20 hours at room temperature under nitrogen. The reaction was diluted with diethylether and washed with 1N HCl, 5% aqueous potassium carbonate solution, brine and was dried over magnesium sulfate. The solution was concentrated under vacuum and the crude product was purified by silica gel chromatography (1:1 hexanes/ethyl acetate). The purified oil was lyophylized to provide 13 mg (12%) of a white powder.  $R_f$  = 0.6 (ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.37-7.14 (8H, m), 6.98 (1H, d), 5.66 (1H, s), 5.03 (1H, m), 4.83 (1H, m), 4.43 (1H, m), 4.33 (4H, d), 4.03-3.79 (6H, m), 3.70 (2H, m), 3.45 (2H, m), 3.29-2.68 (6H, m), 2.06 (2H, m), 1.74-1.46 (3H, m). MS (ESI):  $M+H=635$ .

15

Example 151



(3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl 3-[(1,3-  
20 benzodioxol-5-ylsulfonyl) (tetrahydro-2H-pyran-4-  
yloxy)amino]-1-benzyl-2-hydroxypropylcarbamate.  
(3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-benzyl-  
25 2-hydroxy-3-[(tetrahydro-2H-pyran-4-  
yloxy)amino]propylcarbamate (0.23 mmol, 100 mg) was combined  
1,3-benzodioxole-5-sulfonyl chloride (0.28 mmol, 61 mg),  
diisopropylethylamine (0.69 mmol, 0.12 mL) in anhydrous THF  
(2 mL) and allowed to stir 72 hours at room temperature  
under nitrogen. The reaction was diluted with ethyl acetate  
and washed with 1N HCl, saturated sodium bicarbonate  
30 solution, brine and was dried over magnesium sulfate. The

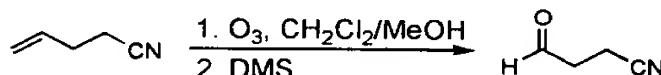
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solution was concentrated under vacuum and the crude product was purified by silica gel chromatography (1:5 hexanes/ethyl acetate). The purified oil was crystallized to provide 55 mg (39%) of white crystals.  $R_f = 0.2$  (1:5 hexanes/ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.38-7.13 (9H, m), 6.90 (1H, d), 6.10 (2H, s), 5.64 (1H, s), 5.02 (1H, m), 4.82 (1H, m), 4.41 (1H, m), 3.99-3.79 (6H, m), 3.72-3.59 (2H, m), 3.49-3.33 (2H, m), 3.25-2.51 (6H, m), 2.09-1.98 (2H, m), 1.69-1.43 (2H, m).  $\text{MS}$  (ESI):  $M+H=621$ .

10

Example 152

Step 1:

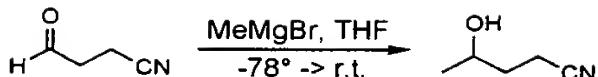


15

**4-oxobutanenitrile.** 4-butenenitrile (43.9 mmol, 3.56 grams) was dissolved in 150 mL of a 3:1 methylene chloride/methanol solution, cooled to  $-78^\circ\text{C}$ , and ozonated until the solution turned blue (15 minutes). The excess ozone was sparged by bubbling nitrogen through the solution while warming to room temperature. Excess dimethylsulfoxide was added and the reaction stirred for 15 hours at room temperature. The reaction was concentrated to a clear liquid, dissolved in ethyl acetate, washed in distilled water, brine and dried over magnesium sulfate. The concentrated crude product was purified by silica gel flash chromatography (2:1 hexanes/ethyl acetate) to provide a brown liquid which was distilled at reduced pressure ( $150^\circ\text{C}/15$  mbar) to provide 2.11 grams (58%) of the purified clear liquid.  $R_f = 0.2$  (2:1 hexanes/ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  9.78 (1H, s), 2.90 (2H, m), 2.61 (2H, m).

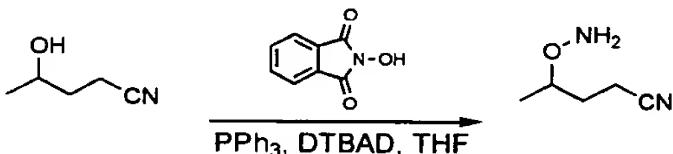
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## Step 2:



5 **4-hydroxypentanenitrile.** The 4-oxobutanenitrile (17.9 mmol, 1.49 grams) was dissolved in anhydrous THF (50 mL) and cooled to -78°C. Methylmagnesium bromide (17.9 mmol, 5.98 mL, 3M in diethyl ether) solution was injected slowly by syringe. The reaction stirred at -78°C for 15 min. and was 10 warmed to room temperature. The reaction was diluted in methylene chloride (50 mL) and dried over magnesium sulfate. The concentrated crude product was purified by silica gel flash chromatography (4:1 methylene chloride/ethyl acetate) and provided 1.2 grams (67%) of the desire alcohol as a 15 yellow liquid.  $R_f = 0.2$  (4:1 methylene chloride/ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  3.91 (1H, m), 2.47 (2H, m), 1.86-1.60 (3H, m), 1.23 (3H, m).

## Step 3:

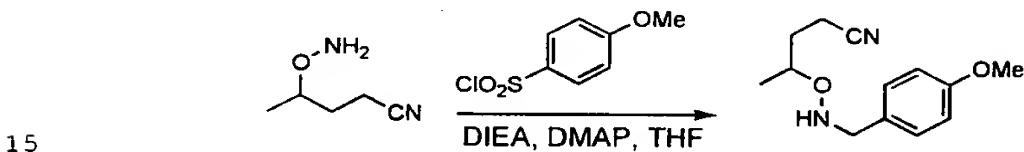


20 **4-(aminoxy)pentanenitrile.** A solution of ditertbutylazodicarboxylate (DTBADM) (13.9 mmol, 3.21 grams) in anhydrous THF (20 mL) was canulated dropwise into a stirring slurry of 4-hydroxypentanenitrile (11.6 mmol, 1.15 grams), *N*-hydroxyphthalimide (11.6 mmol, 1.89 grams), triphenylphosphine (13.9 mmol, 3.65 grams) and anhydrous THF (30 mL). The slurry dissolved on addition and changed color first to orange, then to yellow. The yellow solution stirred at room temperature for 3 hours. The solvent was

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removed under vacuum and the residue was dissolved in TFA. The reaction stirred in TFA for 2 hours to decompose the DTBAD biproduct. The TFA was removed under vacuum and the crude product was dissolved in ethyl acetate, washed in 5 distilled water, 5% aqueous potassium carbonate solution, brine and dried over magnesium sulfate. The crude yellow solid was purified by silica gel flash chromatography (2:1 hexanes/ethyl acetate) and provided 850 mg (32%) of a white crystalline solid.  $R_f = 0.3$  (2:1 hexanes/ethyl acetate); H-  
10 1-NMR ( $CDCl_3$ ):  $\delta$  7.83 (2H, m), 7.76 (2H, m), 4.39 (1H, m), 2.78 (2H, m), 2.03 (2H, m), 1.41 (3H, d).

Step 4:



4-((4-methoxybenzyl)amino)oxy)pentanenitrile

4-(aminoxy)pentanenitrile (1.3 mmol, 150 mg) and 4-methoxybenzenesulfonylchloride (1.3 mmol, 272 mg) were

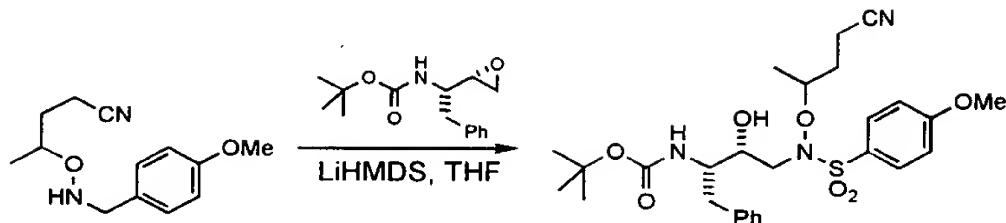
20 combined in anhydrous THF with diisopropylethylamine (1.4 mmol, 0.69 mL) and a few crystals of DMAP. The reaction was stirred at 50°C for 15 hours. The reaction was diluted in diethyl ether, washed with 1N HCl, 1N NaOH and brine and dried over magnesium sulfate. NMR analysis revealed that 25 the isolated crude was the double sulfonyl chloride addition product. The aqueous NaOH fraction was acidified to neutral pH, extracted into ethyl acetate and dried over magnesium sulfate. The solvent was removed under vacuum leaving a very clean 195 mg (52%) crude product.  $R_f = 0.4$  (1:1  
30 hexanes/ethyl acetate); H1-NMR ( $CDCl_3$ ):  $\delta$  7.82 (2H, d), 7.01

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(2H, d), 6.84 (1H, s), 4.17 (1H, m), 3.88 (3H, s), 2.42 (2H, m), 1.88 (2H, m), 1.23 (3H, d).

Step 5:

5

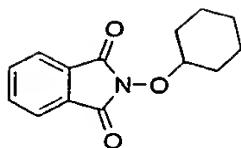


tert-butyl 1-benzyl-3-((3-cyano-1-methylpropoxy)[(4-methoxyphenyl)sulfonyl]amino)-2-hydroxypropylcarbamate. 4-10 {[(4-methoxybenzyl)amino]oxy}pentanenitrile (0.69 mmol, 195 mg) was combined with tert-butyl N-(1S)-1-[(2S)oxiran-2-yl]-2-phenylethylcarbamate (0.57 mmol, 151 mg), lithium bis(trimethylsilyl) amide (0.11 mmol, 0.114 mL, 1.0 M in THF) and anhydrous THF (2 mL). The reaction was stirred 15 under nitrogen at room temperature for 20 hours. The reaction was diluted in ethyl acetate (2 mL) and washed with 1N HCl, saturated aqueous sodium bicarbonate, brine, and was dried over magnesium sulfate. The crude solution was concentrated and purified by silica gel flash chromatography 20 (1:1 hexanes/ethyl acetate) and RP HPLC followed by lyophylization to yield 78 mg (25%) of a white solid.  $R_f = 0.2$  (1:1 hexanes/ethyl acetate);  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.76-7.61 (2H, m), 7.34-7.11 (6H, m), 7.04-6.92 (2H, m), 4.72-4.53 (1H, m), 4.42 (1H, m), 3.89 (3H, s), 3.78 (2H, m), 3.25-2.51 (6H, m), 2.42 (2H, m), 2.02-1.79 (2H, m), 1.43-1.15 (10H, m). 25 MS (ESI):  $M+H=548$ .

### Example 153

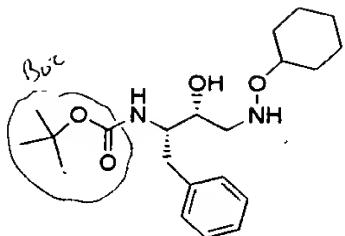
Step 1:

- 280 -



2-(cyclohexyloxy)-1H-isoindole-1,3(2H)-dione. A solution of 5 triphenylphosphine (15.53 g, 59.2 mmol), cyclohexanol (6.25 mL, 59.2 mmol), and N-hydroxypthalimide (9.66 g, 59.2 mmol) in anhydrous tetrahydrofuran (500 mL) under Argon was treated dropwise over approximately 20 minutes with a solution of di-tert-butyl azodicarboxylate (15.00 g, 65.14 mmol) in tetrahydrofuran (100 mL) with a water bath to control the exotherm. After the reddish color had dissipated, a mixture of di-tert-butyl azodicarboxylate (3.00 g, 13.0 mmol) and triphenylphosphine (3.11 g, 11.8 mmol) in anhydrous tetrahydrofuran (50 mL) was added to the 10 reaction mixture and allowed to stir overnight at ambient temperature. After evaporation *in vacuo*, the residue was treated with trifluoroacetic acid (100 mL) and stirred for 20 minutes. The reaction was evaporated *in vacuo* and the residue was partitioned between water and dichloromethane. 15 The layers were separated and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo* to a residue. The crude material was purified twice by flash silica gel chromatography eluting 20 with hexane : ethyl acetate (4:1 and 9:1). Pure fractions were concentrated *in vacuo* to a solid and dried under high vacuum to provide 2-(cyclohexyloxy)-1H-isoindole-1,3(2H)-dione as a solid (10.90 g, 75%). 25

30 Step 2:



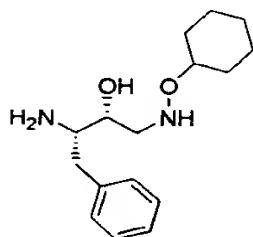
**tert-butyl (1S,2R)-1-benzyl-3-[(cyclohexyloxy)amino]-2-hydroxypropylcarbamate.** A solution 2-(cyclohexyloxy)-1H-isoindole-1,3(2H)-dione (10.00 g, 40.82 mmol) in anhydrous tetrahydrofuran (100 mL) under Argon was treated with anhydrous hydrazine (1.28 mL, 40.82 mmol). After stirring for approximately two hours, the slurry was treated with additional anhydrous hydrazine (0.13 mL, 4.1 mmol). After stirring an additional hour, the reaction mixture was 5 filtered and washed with a minimum quantity of anhydrous tetrahydrofuran. The filtrate was combined with lithium triflate (5.09 g, 32.7 mmol) and tert-butyl N-(1S)-1-[(2S)oxiran-2-yl]-2-phenylethylcarbamate (8.58 g, 32.6 mmol) and brought to reflux. After heating for 16 hours, 10 additional lithium triflate (5.00 g, 32.1 mmol) was added. The reaction was stirred at reflux for an additional 24 hours and then evaporated *in vacuo*. The residue was 15 partitioned between ethyl acetate and water. After separating the layers, the organic phase was washed again with water. The aqueous phases were combined and extracted 20 with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo*. The residue was triturated with diethyl ether and then filtered. The mother liquor was 25 evaporated *in vacuo* and the residue was triturated again with diethyl ether. The second crop was collected by filtration and the mother liquor was evaporated *in vacuo*. The residue was dissolved in diethyl ether and placed in the freezer overnight. A third crop was collected by

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filtration. All three crops were dried under high vacuum to provide tert-butyl (1S,2R)-1-benzyl-3-[(cyclohexyloxy)amino]-2-hydroxypropylcarbamate (4.48 g, 36%) as a solid.  $^1\text{H-NMR}$  (chloroform-D3): 1.34 (m, 14H), 1.52 (m, 1H), 1.72 (m, 2H), 1.95 (m, 2H), 2.97 (m, 4H), 3.25 (m, 1H), 3.67 (m, 1H), 3.83 (m, 1H), 3.92 (m, 1H), 4.32 (b, 1H), 4.61 (d, 1H), 7.26 (m, 5H).  $\text{MS}(\text{ESI})$ : 379 (M+H).

Step 3:

10



(2R,3S)-3-amino-1-[(cyclohexyloxy)amino]-4-phenyl-2-butanol.

A combination of trifluoroacetic acid (20 mL) and tert-butyl (1S,2R)-1-benzyl-3-[(cyclohexyloxy)amino]-2-

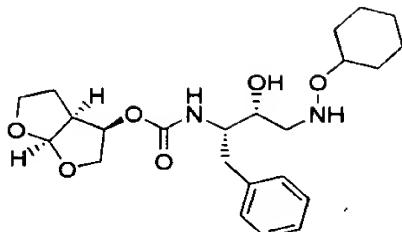
15 hydroxypropylcarbamate (2.00 g, 5.29 mmol) was stirred under Argon at ambient temperature for approximately 30 minutes.

The reaction was evaporated *in vacuo* and the residue was partitioned between dichloromethane and aqueous sodium hydroxide (1N). After separating the layers, the aqueous

20 phase was extracted with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo* to a solid which was dried under high vacuum to provide (2R,3S)-3-amino-1-[(cyclohexyloxy)amino]-4-phenyl-2-butanol (1.426 g, 97%).

25  $^1\text{H-NMR}$  (chloroform-D3): 1.24 (m, 5H), 1.58 (m, 4H), 1.73 (m, 2H), 1.95 (m, 2H), 2.51 (m, 1H), 2.97 (m, 2H), 3.16 (m, 2H), 3.33 (m, 1H), 3.57 (m, 1H), 3.77 (m, 1H), 7.26 (m, 5H).  $\text{MS}(\text{ESI})$ : 279 (M+H).

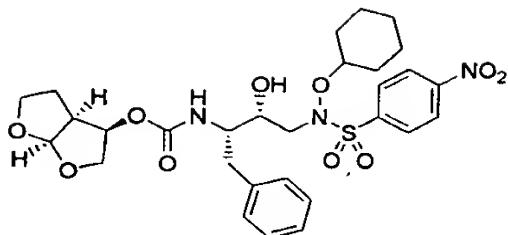
Step 4:



**(3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-benzyl-3-[(cyclohexyloxy)amino]-2-hydroxypropylcarbamate.** A

5 mixture of (2R,3aS,6aR)hexahydrofuro[2,3-b]furan-2-yl 4-nitrophenyl carbonate (1.49 g, 4.82 mmol), (2R,3S)-3-amino-1-[(cyclohexyloxy)amino]-4-phenyl-2-butanol (1.341 g, 4.82 mmol) and diisopropylethylamine (0.841 mL, 4.82 mmol) in acetonitrile (15 mL) under Argon was stirred at ambient  
 10 temperature for 16 hours. The resulting slurry was filtered and washed with cold acetonitrile to provide the first crop of product. The mother liquor was evaporated *in vacuo* dissolved in ethyl acetate and washed twice with aqueous sodium hydroxide (1N). The combined aqueous phases were  
 15 extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The residue was triturated with diethyl ether and filtered to provide a second crop of product. The mother liquor was evaporated *in vacuo* and a third crop was crystallized from the residue  
 20 dissolved *in* a minimum quantity of diethyl ether. The three crops were dried under high vacuum to provide (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-benzyl-3-[(cyclohexyloxy)amino]-2-hydroxypropylcarbamate (1.555 g, 74%). H1-NMR (chloroform-D3): 1.31 (m, 7H), 1.56 (m, 2H), 1.73 (m, 2H), 1.99 (m, 2H), 2.74 (m, 1H), 2.89 (m, 1H), 3.10 (m, 2H), 3.30 (m, 1H), 3.83 (m, 8H), 5.01 (m, 2H), 5.63 (d, 1H), 7.21 (m, 5H). MS(ESI): 456(M+Na).

## Step 5:



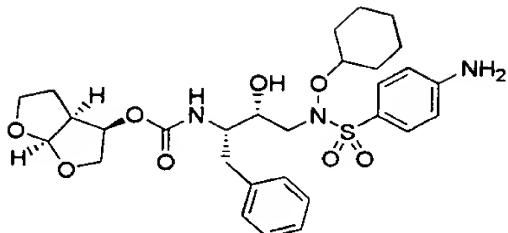
(3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-benzyl-  
 5 3-[(cyclohexyloxy)({(4-nitrophenyl)sulfonyl})amino]-2-  
 hydroxypropylcarbamate. A mixture (3R,3aS,6aR)hexahydrofuro  
 [2,3-b]furan-3-yl (1S,2R)-1-benzyl-3-[(cyclohexyloxy)amino]-  
 10 2-hydroxypropylcarbamate (100 mg, 0.23 mmol), 4-  
 nitrobenzenesulfonyl chloride (61 mg, 0.276 mmol),  
 diisoproylethylamine (0.048 mL, 0.276 mmol) and 4-  
 15 dimethylaminopyridine (~1 mg, cat.) was combined in  
 anhydrous tetrahydrofuran (3 mL) and stirred at ambient  
 temperature under an Argon atmosphere for approximately 16  
 hours. The reaction mixture was evaporated *in vacuo* and the  
 20 residue was partitioned between ethyl acetate and aqueous  
 hydrochloric acid (1N). The organic phase was dried over  
 anhydrous magnesium sulfate, filtered and evaporated *in  
 vacuo*. The residue was purified on flash silica gel  
 eluting with 3:2 hexane : ethyl acetate followed by 1:1  
 25 hexane : ethyl acetate. Fractions containing the product  
 were recombined, evaporated *in vacuo*, and triturated with  
 diethyl ether. The solvent was removed and the residual  
 solid was dried under high vacuum to provide  
 (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-benzyl-  
 3-[(cyclohexyloxy)({(4-nitrophenyl)sulfonyl})amino]-2-  
 hydroxypropylcarbamate (129 mg, 91%). %). H1-NMR  
 (chloroform-D3): 1.22 (m, 7H), 1.64 (m, 2H), 1.78 (m, 2H),  
 2.08 (m, 2H), 2.90 (m, 5H), 3.69 (m, 2H), 3.88 (m, 4H), 4.23  
 (m, 1H), 4.87 (m, 1H), 5.04 (m, 1H), 5.64 (d, 1H), 7.18 (m,

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2H), 7.25 (m, 3H), 7.96 (d, 2H), 8.36 (d, 2H). MS (ESI): 642 (M+Na).

Step 6:

5

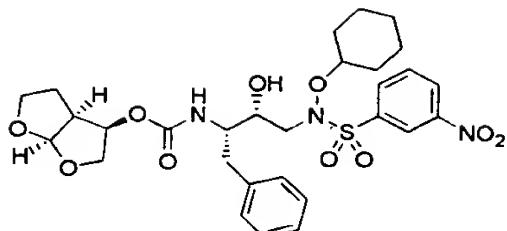


(3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(4-aminophenyl)sulfonyl](cyclohexyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate. To a solution of

10 (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-benzyl-3-[(cyclohexyloxy)[(4-nitrophenyl)sulfonyl]amino]-2-hydroxypropylcarbamate (115 mg, 0.186 mmol) in a 1:1 mixture of ethanol : ethyl acetate (6 mL) was added Palladium on charcoal (10 wt%, 30 mg). The starting material was reduced 15 under an atmosphere of Hydrogen gas over 16 hrs. The reaction mixture was filtered and evaporated *in vacuo*. The residue was purified on a preparative TLC plate (20x20 cm, 500  $\mu$ M) eluting with 3:1 ethyl acetate : hexane. The product band was removed, eluted with 3:1 methylene chloride 20 : methanol, filtered, and evaporated *in vacuo*. The residue was triturated with water, filtered and dried under high vacuum to provide (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(4-aminophenyl)sulfonyl](cyclohexyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate (89 mg, 81%).  $^1$ H-NMR 25 (chloroform-D3): 1.26 (m, 6H), 1.58 (m, 5H), 2.05 (m, 2H), 2.90 (m, 4H), 3.09 (b, 2H), 3.68 (m, 2H), 3.88 (m, 4H), 4.16 (m, 1H), 4.24 (b, 1H), 4.81 (d, 1H), 5.00 (m, 1H), 5.63 (d, 1H), 6.66 (d, 2H), 7.23 (m, 5H), 7.56 (d, 2H). MS (ESI): 612 (M+Na).

Example 154

Step 1:



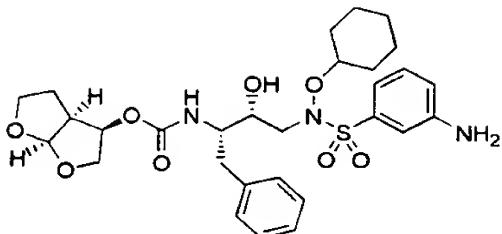
5 (3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-benzyl-3-[(cyclohexyloxy)amino]-2-hydroxypropylcarbamate. A mixture  
 (3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-benzyl-3-[(cyclohexyloxy)amino]-2-hydroxypropylcarbamate (342 mg,  
 10 0.788 mmol), 3-nitrobenzenesulfonyl chloride (175 mg, 0.788 mmol) and diisopropylethylamine (0.137 mL, 0.867 mmol) was combined in anhydrous tetrahydrofuran (10 mL) and stirred at ambient temperature under an Argon atmosphere for approximately 40 hours. The reaction mixture was  
 15 partitioned between ethyl acetate and aqueous hydrochloric acid (1N). After separating the phases, the aqueous layer was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous magnesium sulfate, and evaporate *in vacuo*. The residue was  
 20 purified on flash grade silica gel eluting with 1:1 ethyl acetate : hexane. The fractions containing the product were combined, evaporated *in vacuo* and dried under high vacuum to provide (3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-benzyl-3-[(cyclohexyloxy)amino]-2-hydroxypropylcarbamate (428 mg, 88%) as a foam.  $^1\text{H-NMR}$  (chloroform-D3): 1.29 (m, 6H), 1.57 (m, 3H), 1.76 (m, 2H), 2.08 (m, 2H), 2.91 (m, 4H), 3.10 (b, 1H), 3.68 (m, 2H), 3.88 (m, 4H), 4.25 (m, 1H), 4.83 (d, 1H), 5.00 (m, 1H), 5.64 (d,

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1H), 7.22 (m, 5H), 7.76 (m, 1H), 8.07 (d, 1H), 8.50 (d, 1H), 8.66 (s, 1H). MS (ESI): 642 (M+Na).

Step 2:

5

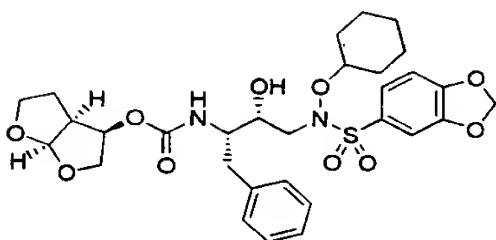


(3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(3-aminophenyl)sulfonyl](cyclohexyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate. A solution of

10 (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-benzyl-3-[(cyclohexyloxy)(3-nitrophenyl)sulfonyl]amino]-2-hydroxypropylcarbamate (403 mg, 0.651 mmol) in absolute ethanol (12 mL) was combined with Palladium on carbon (10 wt%, 80 mg) and reduced under a Hydrogen atmosphere for 16 hours. The reaction mixture was filtered and evaporated *in vacuo* to provide (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(3-aminophenyl)sulfonyl](cyclohexyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate (356 mg, 93%) as a foam. A sample of the product (30 mg) was purified on a preparative 15 TLC plate (20x20 cm, 500  $\mu$ M) eluting with 95:5 dichloromethane : methanol. The product band was removed, eluted with 3:1 methylene chloride : methanol, filtered, and evaporated *in vacuo*. The residue was triturated with water, filtered and dried under high vacuum to provide 20 (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(3-aminophenyl)sulfonyl](cyclohexyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate (18 mg) as a solid.  $^1$ H-NMR (chloroform-D3): 1.26 (m, 6H), 1.64 (m, 5H), 2.07 (m, 2H), 2.93 (m, 4H), 3.14 (b, 1H), 3.69 (m, 2H), 3.87 (m, 4H), 3.94

(b, 2H), 4.19 (m, 1H), 4.83 (b, 1H), 5.03 (m, 1H), 5.64 (d, 1H), 6.89 (d, 1H), 7.06 (s, 1H), 7.21 (m, 7H). MS(ESI): 612 (M+Na).

5

Example 155

(3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(cyclohexyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate. A mixture of

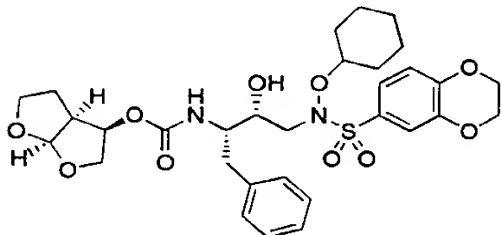
10 (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-benzyl-3-[(cyclohexyloxy)amino]-2-hydroxypropylcarbamate (100 mg, 0.230), 1,3-benzodioxole-5-sulfonyl chloride (Eur. Pat. Appl. 583960, 23 Feb 1994, 56 mg, 0.253 mmol) and diisoproylethylamine (0.042 mL, 0.242 mmol) in anhydrous tetrahydrofuran (3 mL) was stirred at ambient temperature under an Argon atmosphere for 16 hours. A catalytic quantity of dimethylaminopyridine (~1 mg) was added and the reaction was heated at reflux for approximately 2 hours. An additional quantity of 1,3-benzodioxole-5-sulfonyl chloride (11 mg, 0.050 mmol) was added and the reaction was heated for an additional hour. After cooling to ambient temperature, the reaction mixture was partitioned between ethyl acetate and aqueous hydrochloric acid. After separating the phases, the organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified on a preparative TLC plate (20x20 cm, 500  $\mu$ M) eluting with 1:1 ethyl acetate : hexane. The product band was removed, eluted with 3:1 methylene chloride : methanol, filtered, and

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evaporated *in vacuo*. The residue was triturated with water, filtered and dried under high vacuum to provide (3*R*, 3*aS*, 6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*, 2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(cyclohexyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate (123 mg, 87%) as a white solid. *H*1-NMR (chloroform-D3): 1.32 (m, 6H), 1.70 (m, 5H), 2.14 (m, 2H), 3.00 (m, 4H), 3.18 (b, 1H), 3.74 (m, 2H), 3.97 (m, 4H), 4.27 (m, 1H), 4.90 (m, 1H), 5.07 (m, 1H), 5.70 (d, 1H), 6.15 (s, 2H), 6.95 (d, 1H), 7.30 (m, 7H). MS (ESI): 641 (M+Na).

10

Example 156



(3*R*, 3*aS*, 6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*, 2*R*)-1-benzyl-3-[(cyclohexyloxy)(2,3-dihydro-1,4-benzodioxin-6-ylsulfonyl)amino]-2-hydroxypropylcarbamate. A mixture of 1,4-benzodioxan-6-sulfonyl chloride (Eur. Pat. Appl. 583960, 23 Feb 1994; 60 mg; 0.253 mmol), (3*R*, 3*aS*, 6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*, 2*R*)-1-benzyl-3-[(cyclohexyloxy)amino]-2-hydroxypropylcarbamate (100 mg, 0.230 mmol), and diisoproylethylamine (0.042 mL, 0.242 mmol) in anhydrous tetrahydrofuran (3 mL) was stirred at ambient temperature under an Argon atmosphere for 16 hours. A catalytic quantity of dimethylaminopyridine (~1 mg) was added and the reaction was heated at reflux for approximately 2 hours. An additional quantity of 1,4-benzodioxan-6-sulfonyl chloride (12 mg, 0.051 mmol) was added and the reaction was heated for an additional 30 minutes. After cooling to ambient temperature, the reaction mixture was partitioned between ethyl acetate and aqueous

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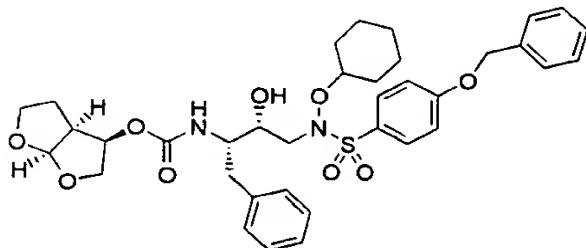
hydrochloric acid. After separating the phases, the organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified on a preparative TLC plate (20x20 cm, 500  $\mu$ M)

5 eluting with 1:1 ethyl acetate : hexane. The product band was removed, eluted with 3:1 methylene chloride : methanol, filtered, and evaporated *in vacuo*. The residue was triturated with water, filtered and dried under high vacuum to provide (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl

10 (1S,2R)-1-benzyl-3-[(cyclohexyloxy)(2,3-dihydro-1,4-benzodioxin-6-ylsulfonyl)amino]-2-hydroxypropylcarbamate (125 mg, 86%) as a white solid. H1-NMR (chloroform-D3): 1.20 (m, 6H), 1.60 (m, 5H), 2.07 (m, 2H), 2.90 (m, 4H), 3.09 (b, 1H), 3.67 (m, 2H), 3.90 (m, 4H), 4.23 (m, 1H), 4.31 (m, 4H), 4.82 (d, 1H), 5.01 (m, 1H), 5.64 (d, 1H), 6.95 (d, 1H) 7.25 (m, 7H). MS(ESI): 655 (M+Na).

15

Example 157



20 (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-benzyl-3-[(4-(benzyloxy)phenyl)sulfonyl](cyclohexyloxy)amino]-2-hydroxypropylcarbamate.

A mixture of 4-benzyloxybenzenesulfonyl chloride (65 mg; 0.230 mmol), (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-benzyl-3-[(cyclohexyloxy)amino]-2-hydroxypropylcarbamate (100 mg, 0.230 mmol), diisoproylethylamine (0.042 mL, 0.242 mmol) and 4-

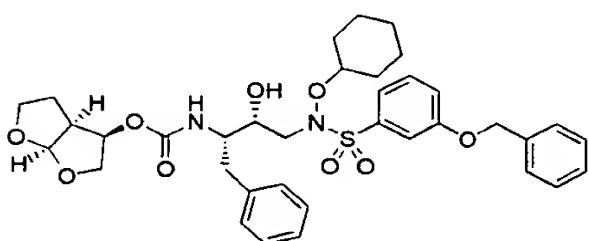
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dimethylaminopyridine (~1 mg) in anhydrous tetrahydrofuran (3 mL) was stirred at ambient temperature under an Argon atmosphere for 16 hours. An additional quantity of 4-benzyloxybenzenesulfonyl chloride (13 mg, 0.046 mmol) and 4-dimethylaminopyridine (~1 mg) was added and the reaction was heated at reflux for approximately 2 hours. After cooling to ambient temperature, the reaction mixture was partitioned between ethyl acetate and aqueous hydrochloric acid. The phases were separated and the organic layer was then washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The crude product was purified on flash grade silica gel eluting with 1:1 ethyl acetate : hexane. Fractions containing the product were combined and evaporated *in vacuo* and dried under high vacuum to provide (3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-benzyl-3-[(4-benzyloxyphenyl)sulfonyl](cyclohexyloxy)amino]-2-hydroxypropylcarbamate (143 mg, 91%). <sup>1</sup>H-NMR (chloroform-D3): 1.27 (m, 6H), 1.61 (m, 5H), 2.07 (m, 2H), 2.91 (m, 4H), 3.10 (b, 1H), 3.68 (m, 2H), 3.89 (m, 4H), 4.19 (m, 1H), 4.84 (m, 1H), 5.01 (m, 1H), 5.12 (s, 2H), 5.64 (d, 1H), 7.05 (d, 2H), 7.28 (m, 10H), 7.71 (d, 2H). MS (ESI): 703 (M+Na).

Example 158

25



(3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-benzyl-3-[(4-benzyloxyphenyl)sulfonyl](cyclohexyloxy)amino]-2-hydroxypropylcarbamate.

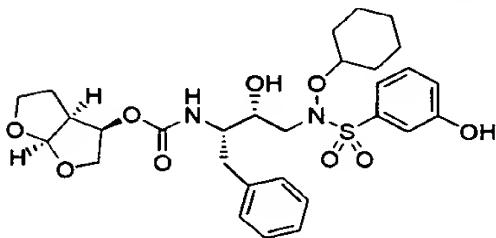
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A mixture of 3-benzyloxybenzenesulfonyl chloride (65 mg, 0.230 mmol), (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-benzyl-3-[(cyclohexyloxy)amino]-2-hydroxypropylcarbamate (100 mg, 0.230 mmol) and 5 diisopropylethylamine (0.042 mL, 0.242 mmol) in anhydrous tetrahydrofuran (3 mL) was stirred at ambient temperature under an Argon atmosphere for 16 hours. A catalytic quantity of dimethylaminopyridine (~1 mg) was added and the reaction was heated at reflux for approximately one hour.

10 An additional quantity of 3-benzyloxybenzenesulfonyl chloride (13 mg, 0.046 mmol) was added and the reaction was heated at reflux for approximately 1 hour. After cooling to ambient temperature, the reaction mixture was partitioned between ethyl acetate and aqueous hydrochloric acid. The 15 phases were separated and the organic layer was then washed with brine, dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The residue was dried under high vacuum to provide (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-benzyl-3-[(3-(benzyloxy)phenyl)sulfonyl] (cyclohexyloxy)amino]-2-hydroxypropylcarbamate (140 mg, 20 89%). <sup>1</sup>H-NMR (chloroform-D3): 1.22 (m, 6H), 1.62 (m, 5H), 2.05 (m, 2H), 2.90 (m, 4H), 3.11 (b, 1H), 3.66 (m, 2H), 3.87 (m, 4H), 4.18 (m, 1H), 4.77 (m, 1H), 4.95 (m, 1H), 5.10 (m, 2H), 5.60 (d, 1H), 7.29 (m, 14H). MS(ESI): 703 (M+Na).

25

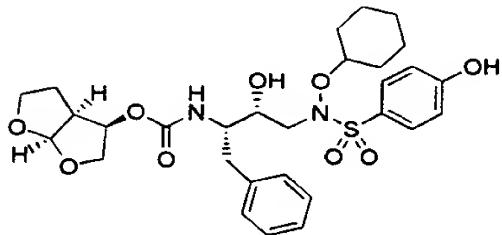
Example 159



(3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-benzyl-3-[(cyclohexyloxy)amino]-2-

**hydroxypropylcarbamate.** A solution of (3*R*, 3a*S*, 6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*, 2*R*)-1-benzyl-3-[(3-(benzyloxy)phenyl)sulfonyl](cyclohexyloxy)amino]-2-hydroxypropylcarbamate (131 mg, 0.193 mmol) in ethyl acetate (~5 mL) was combined with Palladium on carbon (10 wt%, 25 mg) and reduced under an atmosphere of Hydrogen gas. After stirring for 16 hours, the reaction mixture was filtered and evaporated *in vacuo* to a residue. The residue was purified on a preparative TLC plate (20x20 cm, 500  $\mu$ M) eluting with 3:2 ethyl acetate : hexane. The product band was removed, eluted with 3:1 methylene chloride : methanol, filtered, and evaporated *in vacuo*. The residue was triturated with water, filtered and dried under high vacuum to provide (3*R*, 3a*S*, 6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*, 2*R*)-1-benzyl-3-[(cyclohexyloxy)(3-hydroxyphenyl)sulfonyl]amino]-2-hydroxypropylcarbamate (93 mg, 82%) as a white solid.  $^1$ H-NMR (chloroform-D3): 1.28 (m, 6H), 1.67 (m, 5H), 2.06 (m, 2H), 2.96 (m, 4H), 3.09 (b, 1H), 3.87 (m, 6H), 4.19 (m, 1H), 5.01 (m, 2H), 5.69 (d, 1H), 6.60 (b, 1H), 7.23 (m, 9H). 20 MS (ESI): 613 (M+Na).

Example 160



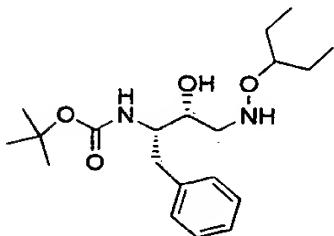
**25 (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-benzyl-3-[(cyclohexyloxy)(4-hydroxyphenyl)sulfonyl]amino]-2-hydroxypropylcarbamate.** A solution of (3*R*, 3a*S*, 6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*, 2*R*)-1-benzyl-3-[(4-(benzyloxy)phenyl)sulfonyl](cyclohexyloxy)amino]-2-hydroxypropylcarbamate (140 mg, 0.206 mmol) in ethyl acetate

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(5 mL) was combined with Palladium on carbon (10 wt%, 28 mg) and reduced under an atmosphere of Hydrogen gas. After stirring for 16 hours, the reaction mixture was filtered and evaporated *in vacuo* to a residue. The residue was purified 5 on a preparative TLC plate (20x20 cm, 500  $\mu$ M) eluting with 3:2 ethyl acetate : hexane. The product band was removed, eluted with 4:1 methylene chloride : methanol, filtered, and evaporated *in vacuo*. The residue was triturated with water, filtered and dried under high vacuum to provide 10 (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-benzyl-3-[(cyclohexyloxy)[(4-hydroxyphenyl)sulfonyl]amino]-2-hydroxypropylcarbamate (106 mg, 87%) as a white solid.  $^1$ H-NMR (chloroform-D3): 1.27 (m, 6H), 1.67 (m, 5H), 2.05 (m, 2H), 2.93 (m, 4H), 3.11 (b, 1H), 3.68 (m, 2H), 3.90 (m, 4H), 15 4.19 (m, 1H), 4.81 (d, 1H), 4.99 (m, 1H), 5.65 (d, 1H), 6.24 (b, 1H), 6.92 (d, 2H), 7.22 (m, 5H), 7.67 (d, 2H). MS(ESI): 613 (M+Na).

Example 161

20 Step 1:

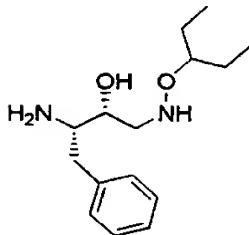


tert-butyl (1S,2R)-1-benzyl-3-[(1-ethylpropoxy)amino]-2-hydroxypropylcarbamate. A solution of 2-(1-ethylpropoxy)-25 1H-isoindole-1,3(2H)-dione [Synth. Comm., 22(10), 1427-1432 (1992), 10.00 g, 42.9 mmol] in anhydrous tetrahydrofuran (100 mL) under Argon was treated with anhydrous hydrazine (1.48 mL, 47.2 mmol) over approximately 5 minutes. The reaction was stirred for 45 minutes and diluted with

- 295 -

anhydrous tetrahydrofuran (50 mL). An additional quantity of anhydrous hydrazine (0.888 mL, 28.3 mmol) was added in six increments over 90 minutes. The mixture was filtered washing with tetrahydrofuran (~50 mL). The mother liquor 5 was combined with tert-butyl N-(1S)-1-[(2S)oxiran-2-yl]-2-phenylethylcarbamate (9.03 g, 34.3 mmol) and lithium triflate (5.36 g, 34.3 mmol) and heated to reflux. After stirring for 3.5 days, the reaction was evaporated *in vacuo* and the residue was partitioned between aqueous potassium 10 carbonate (5% w/v) and ethyl acetate. The aqueous phase was separated and extracted with ethyl acetate. The combined organic layers were washed with saturated brine, dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified on flash grade silica gel eluting with 15 3:1 hexane : ethyl acetate. Fractions containing the product were evaporated *in vacuo* and dried under high vacuum to tert-butyl (1S,2R)-1-benzyl-3-[(1-ethylpropoxy)amino]-2-hydroxypropylcarbamate (6.425 g, 51%) as a solid.  $^1\text{H-NMR}$  (chloroform-D3): 0.88 (m, 6H), 1.34 (s, 9H), 1.51 (m, 4H), 2.91 (m, 4H), 3.15 (d, 1H), 3.47 (m, 1H), 3.69 (m, 2H), 3.89 (m, 1H), 4.57 (m, 1H), 7.24 (m, 5H). MS (ESI): 389 (M+Na). 20

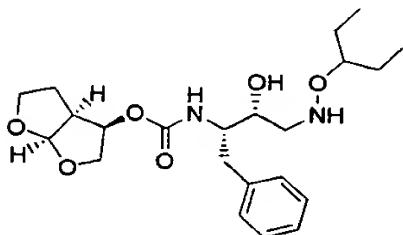
Step 2:



(2R,3S)-3-amino-1-[(1-ethylpropoxy)amino]-4-phenyl-2-  
25 butanol. A mixture of tert-butyl (1S,2R)-1-benzyl-3-[(1-ethylpropoxy)amino]-2-hydroxypropylcarbamate (3.285 g, 8.98 mmol) and trifluoroacetic acid (25 mL) was stirred at ambient temperature under Argon for approximately 30 minutes. The reaction was evaporated *in vacuo* and the

residue was partitioned between dichloromethane and aqueous sodium hydroxide (1N). The phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate, filter, evaporated *in vacuo* and dried under high vacuum to provide (2*R*,3*S*)-3-amino-1-[(1-ethylpropoxy)amino]-4-phenyl-2-butanol (2.455 g, 100%) as a solid.  $^1\text{H-NMR}$  (chloroform-D3): 0.94 (m, 6H), 1.56 (m, 4H), 2.55 (m, 1H), 3.01 (m, 2H), 3.22 (m, 2H), 3.51 (m, 1H), 3.81 (m, 1H), 7.30 (m, 5H). MS(ESI): 267(M+H).  
10

## Step 3:

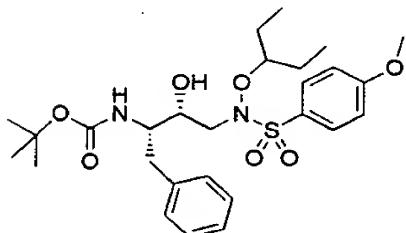


(3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-benzyl-15 3-[(1-ethylpropoxy)amino]-2-hydroxypropylcarbamate. A mixture of (2*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-2-yl 4-nitrophenyl carbonate (2.764 g, 8.94 mmol), (2*R*,3*S*)-3-amino-1-[(1-ethylpropoxy)amino]-4-phenyl-2-butanol (2.379 g, 8.94 mmol), and diisopropylethylamine (1.56 mL, 8.94 mmol) in 20 acetonitrile (25 mL) under Argon was stirred at ambient temperature for 16 hours. The reaction mixture was evaporated *in vacuo* and the residue was partitioned between ethyl acetate and aqueous potassium carbonate (5% w/v). The phases were separated and the organic layer was washed again 25 with aqueous potassium carbonate (5% w/v). The aqueous phases were combined and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and evaporated *in vacuo*. The residue was triturated with diethyl ether and filtered. The

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mother liquor was evaporated *in vacuo* and the residue was purified on flash grade silica gel eluting with 1:1 ethyl acetate : hexane. Fractions containing the product were combined and evaporated *in vacuo* to a solid. Both crops of 5 product were dried under high vacuum to provide (3*R*, 3a*S*, 6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*, 2*R*)-1-benzyl-3-[(1-ethylpropoxy)amino]-2-hydroxypropylcarbamate (2.554 g, 68%). <sup>1</sup>H-NMR (chloroform-D3): 0.88 (m, 6H), 1.52 (m, 7H), 2.77 (m, 1H), 2.91 (m, 2H), 3.07 (m, 1H), 3.16 (m, 1H), 3.37 10 (b, 1H), 3.46 (m, 1H), 3.75 (m, 4H), 3.94 (m, 2H), 4.87 (d, 1H), 5.03 (m, 1H), 5.63 (d, 1H), 7.23 (m, 5H). MS(ESI): 445(M+Na).

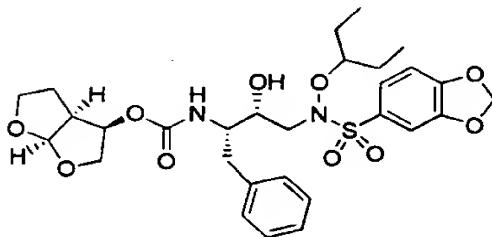
## Step 4:



15 **tert-butyl (1*S*,2*R*)-1-benzyl-3-[(1-ethylpropoxy)amino]-2-hydroxypropylcarbamate.** A mixture of *tert*-butyl (1*S*,2*R*)-1-benzyl-3-[(1-ethylpropoxy)amino]-2-hydroxypropylcarbamate (100 mg, 0.273 mmol), 4-methoxyphenylsulphonyl chloride (57 mg, 0.273 mmol), and diisopropylethylamine (0.0476 mL, 0.273 mmol) in anhydrous tetrahydrofuran (2 mL) was stirred under Argon for 16 hours at ambient temperature. A catalytic quantity of 4-dimethylaminopyridine (~1 mg) was added and the reaction was 20 heated at reflux for approximately two hours. After cooling, the reaction was evaporated *in vacuo* and the residue was dissolved in ethyl acetate. The solution was washed with aqueous potassium carbonate (5% w/v), aqueous hydrochloric acid (1N) and brine. The organic layer was 25

then dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified on a preparative TLC plate (20x20 cm, 500  $\mu$ M) eluting with 95:5 methylene chloride : methanol. The product band was 5 removed, eluted with 4:1 methylene chloride : methanol, filtered, and evaporated *in vacuo*. The residue was purified again on a preparative TLC plate (20x20 cm, 500  $\mu$ M) eluting with 95:5 methylene chloride : ethyl acetate. The product band was removed, eluted with 4:1 methylene chloride : 10 methanol, filtered, and evaporated *in vacuo* to provide tert-butyl (1*S*,2*R*)-1-benzyl-3-[(1-ethylpropoxy){(4-methoxyphenyl)sulfonyl}amino]-2-hydroxypropylcarbamate (103 mg, 70%) as a foam.  $^1$ H-NMR (chloroform-D3): 0.95 (m, 6H), 1.38 (s, 9H), 1.64 (m, 4H), 3.01 (m, 5H), 3.83 (m, 2H), 3.93 15 (s, 3H), 4.20 (m, 1H), 4.61 (m, 1H), 7.03 (d, 2H), 7.29 (m, 5H), 7.80 (d, 2H). MS(ESI): 559 (M+Na).

Example 162



20 (3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(1-ethylpropoxy)amino]-1-benzyl-2-hydroxypropylcarbamate. A mixture of (3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-benzyl-3-[(1-ethylpropoxy)amino]-2-hydroxypropylcarbamate (0.100 g, 25 0.237 mmol), 1,3-benzodioxole-5-sulfonyl chloride (52 mg, 0.237 mmol), diisopropylethylamine (0.042 mL, 0.237 mmol) and dimethylaminopyridine (~1 mg) in anhydrous tetrahydrofuran (3 mL) was stirred at ambient temperature over 16 hours

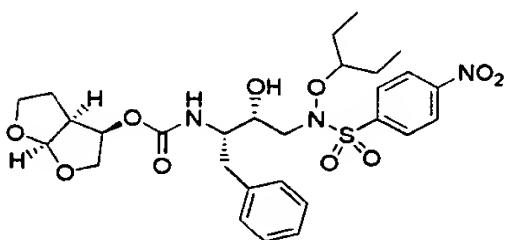
- 299 -

under an Argon atmosphere. The reaction was evaporated *in vacuo* and the residue was partitioned between dichloromethane and aqueous hydrochloric acid (1N). The organic phase was separated and dried over anhydrous 5 magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified on a preparative TLC plate (20x20 cm, 500  $\mu$ M) eluting with 97:3 dichloromethane : methanol. The product band was removed, eluted with 4:1 methylene chloride : methanol, filtered, and evaporated *in vacuo*. The residue 10 was triturated with water, filtered and dried under high vacuum to provide (3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(1-ethylpropoxy)amino]-1-benzyl-2-hydroxypropylcarbamate (114 mg, 80%) as a white solid.  $^1$ H-NMR (chloroform-D3): 0.89 (m, 6H), 1.57 (m, 7H), 2.95 (m, 5H), 3.69 (m, 2H), 3.89 (m, 4H), 4.15 (m, 1H), 4.82 (d, 1H), 5.01 (m, 1H), 5.64 (d, 1H), 6.10 (s, 2H), 6.90 (d, 1H), 7.23 (m, 6H), 7.39 (m, 1H). MS (ESI): 15 629 (M+Na).

20

Example 163

Step 1:



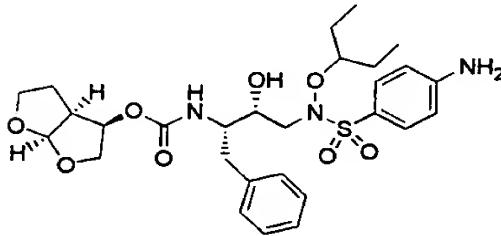
25 (3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-benzyl-3-[(1-ethylpropoxy)amino]-2-hydroxypropylcarbamate. A mixture of (3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-benzyl-3-[(1-ethylpropoxy)amino]-2-hydroxypropylcarbamate (200 mg, 0.474 mmol), 4-nitrophenylsulphonyl chloride (105 mg, 0.474 mmol), diisoproylethylamine (0.084 mL, 0.474 mmol) and

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dimethylaminopyridine (~1 mg) in anhydrous tetrahydrofuran (3 mL) was stirred at ambient temperature over 16 hours under an Argon atmosphere. The reaction was evaporated *in vacuo* and the residue was partitioned between 5 dichloromethane and aqueous sodium hydrogen sulfate (1N). The phases were separated and the aqueous layer was extracted with dichloromethane. The combined organic phases were dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified on flash 10 grade silica gel eluting with 1:1 ethyl acetate : hexane. Fractions containing the product were combined, evaporated *in vacuo* and dried under high vacuum to provide (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-benzyl-3-((1-ethylpropoxy){(4-nitrophenyl)sulfonyl}amino)-2- 15 hydroxypropylcarbamate (254 mg, 88%) as a foam.  $^1\text{H-NMR}$  (chloroform-D3): 0.90 (m, 6H), 1.60 (m, 7H), 2.90 (m, 5H), 3.68 (m, 2H), 3.87 (m, 4H), 4.17 (m, 1H), 4.83 (d, 1H), 5.02 (m, 1H), 5.64 (d, 1H), 7.23 (m, 5H), 7.99 (d, 2H), 8.38 (d, 2H). MS (ESI): 630 (M+Na).

20

Step 2:



(3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(4-aminophenyl)sulfonyl](1-ethylpropoxy)amino]-1-benzyl-2- 25 hydroxypropylcarbamate. A solution of (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-benzyl-3-((1-ethylpropoxy){(4-nitrophenyl)sulfonyl}amino)-2-hydroxypropylcarbamate (237 mg, 0.390 mmol) in absolute methanol (5 mL) was combined with Palladium on carbon (10

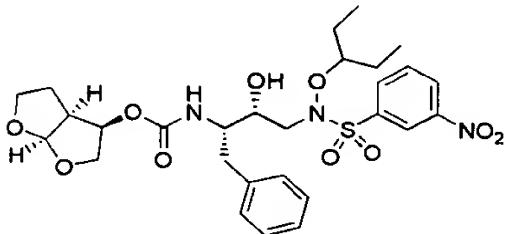
- 301 -

wt%, 50 mg) and reduced under a Hydrogen atmosphere over 16 hours. The reaction was filtered and evaporated *in vacuo*. The residue was purified on silica gel eluting with 50-60% ethyl acetate in hexane. Fractions containing the product 5 were combined and evaporated *in vacuo*. The residue was triturated with water, filtered and dried under high vacuum to provide (3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-[(4-aminophenyl)sulfonyl](1-ethylpropoxy)amino]-10 1-benzyl-2-hydroxypropylcarbamate (160 mg, 71%) as a white solid.  $^1\text{H-NMR}$  (chloroform-D3): 0.90 (m, 6H), 1.58 (m, 7H), 2.95 (m, 5H), 3.69 (m, 2H), 3.91 (m, 4H), 4.13 (m, 1H), 4.26 (b, 2H), 4.80 (d, 1H), 5.00 (m, 1H), 5.63 (d, 1H), 6.67 (d, 2H), 7.22 (m, 5H), 7.58 (d, 2H). MS(ESI): 600(M+Na).

15

Example 164

Step 1:



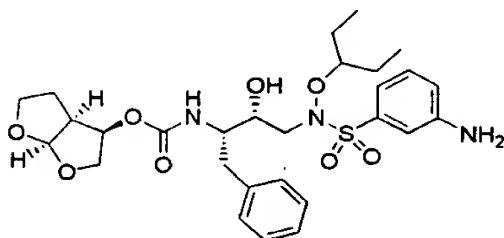
**Preparation of (3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-benzyl-3-[(1-ethylpropoxy)amino]-2-hydroxypropylcarbamate.**

20 A mixture of (3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-benzyl-3-[(1-ethylpropoxy)amino]-2-hydroxypropylcarbamate (200 mg, 0.474 mmol), 3-nitrophenylsulphonyl chloride (105 mg, 0.474 mmol), 25 diisopropylethylamine (0.084 mL, 0.474 mmol) and dimethylaminopyridine (~1 mg) in anhydrous tetrahydrofuran (3 mL) was stirred at ambient temperature over 16 hours under an Argon atmosphere. The reaction was evaporated *in vacuo* and the residue was partitioned between

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dichloromethane and aqueous hydrochloric acid (1N). After separating the phases, the aqueous layer was extracted with dichloromethane. The combined organic phases were dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified on flash grade silica gel eluting with 1:1 ethyl acetate : hexane. Fractions containing the product were combined, evaporated *in vacuo* and dried under high vacuum to provide (3*R*, 3*aS*, 6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*, 2*R*)-1-benzyl-3-[(1-ethylpropoxy) [(3-nitrophenyl)sulfonyl]amino]-2-hydroxypropylcarbamate (246 mg, 86%).  $^1\text{H-NMR}$  (chloroform-D3): 0.98 (m, 6H), 1.68 (m, 7H), 2.99 (m, 5H), 3.73 (m, 2H), 3.96 (m, 4H), 4.27 (m, 1H), 4.86 (d, 1H), 5.07 (m, 1H), 5.69 (d, 1H), 7.27 (m, 5H), 7.84 (m, 1H), 8.16 (d, 1H), 8.57 (d, 1H), 8.76 (s, 1H).  $\text{MS}(\text{ESI})$ : 630(M+Na).

Step 2:

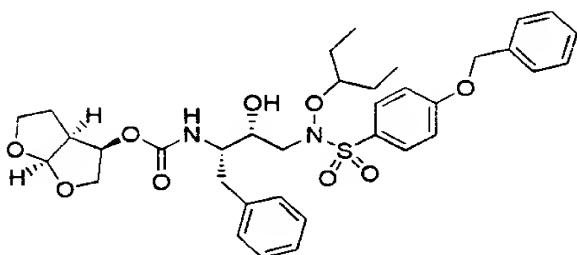


(3*R*, 3*aS*, 6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*, 2*R*)-3-[(3-aminophenyl)sulfonyl](1-ethylpropoxy)amino]-1-benzyl-2-hydroxypropylcarbamate. A solution of (3*R*, 3*aS*, 6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*, 2*R*)-1-benzyl-3-[(1-ethylpropoxy) [(3-nitrophenyl)sulfonyl]amino]-2-hydroxypropylcarbamate (239 mg, 0.394 mmol) in absolute ethanol (3 mL) was combined with Palladium on carbon (10 wt%, 25 mg) and reduced under a Hydrogen atmosphere over 16 hours. The reaction was filtered and evaporated *in vacuo*. The residue was purified on flash grade silica gel eluting with 3:2 ethyl acetate : hexane. Fractions containing the

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product were combined and evaporated *in vacuo*. The residue was triturated with water, filtered and dried under high vacuum to provide (3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-[(3-aminophenyl)sulfonyl](1-5 ethylpropoxy)amino]-1-benzyl-2-hydroxypropylcarbamate (153 mg, 67%) as a white solid.  $^1\text{H-NMR}$  (chloroform-D3): 0.96 (m, 6H), 1.62 (m, 7H), 3.05 (m, 5H), 3.76 (m, 2H), 3.96 (m, 6H), 4.19 (m, 1H), 4.88 (m, 1H), 5.07 (m, 1H), 5.69 (d, 1H), 6.95 (d, 1H), 7.14 (s, 1H), 7.28 (m, 7H).  $\text{MS(ESI)}$ : 10 600 (M+Na).

Example 165



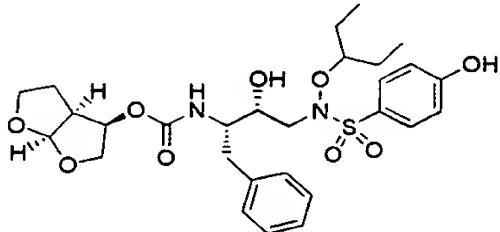
15 (3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-benzyl-3-[(4-(benzyloxy)phenyl)sulfonyl](1-ethylpropoxy)amino]-2-hydroxypropylcarbamate. A mixture of (3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-benzyl-3-[(1-ethylpropoxy)amino]-2-hydroxypropylcarbamate (200 mg, 20 0.474 mmol), 4-benzyloxybenzenesulphonyl chloride (134 mg, 0.474 mmol), diisoproylethylamine (0.083 mL, 0.474 mmol) and dimethylaminopyridine (~1 mg) in anhydrous tetrahydrofuran (3 mL) was stirred at ambient temperature over 16 hours under an Argon atmosphere. The reaction mixture was warmed 25 to 55°C and an additional quantity of dimethylaminopyridine (~2 mg) was added. After stirring for 2 hours, the reaction was evaporated *in vacuo* and the residue was partitioned between dichloromethane and aqueous sodium hydrogen sulfate

- 304 -

(1N). After separating the phases, the aqueous layer was extracted with dichloromethane. The combined organic phases were dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo*. The residue was purified on flash 5 grade silica gel eluting with 3:2 ethyl acetate : hexane. Fractions containing the product were combined, evaporated *in vacuo*, and dried under high vacuum to provide (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-benzyl-3-[(4-(benzyloxy)phenyl)sulfonyl](1-ethylpropoxy)amino]-2-10 hydroxypropylcarbamate (235 mg, 74%) as a foam.  $^1\text{H-NMR}$  (chloroform-D3): 0.94 (m, 6H), 1.62 (m, 7H), 3.05 (m, 5H), 3.74 (m, 2H), 3.98 (m, 4H), 4.18 (m, 1H), 4.88 (d, 1H), 5.08 (m, 1H), 5.19 (s, 2H), 5.70 (d, 1H), 7.13 (d, 2H), 7.34 (m, 10H), 7.80 (d, 2H).  $\text{MS}(\text{ESI})$ : 691 (M+Na).

15

Example 166



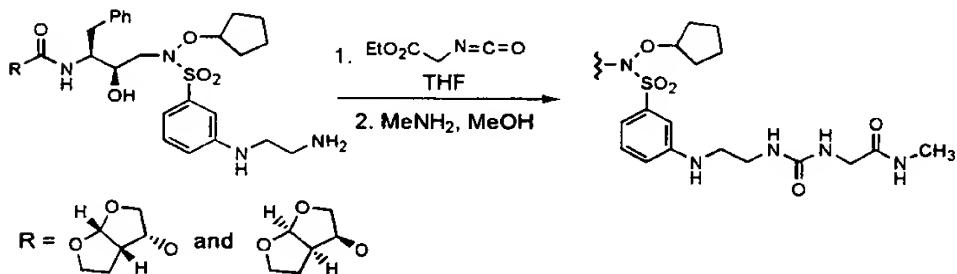
(3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-benzyl-3-[(1-ethylpropoxy) [(4-hydroxyphenyl)sulfonyl]amino]-2-20 hydroxypropylcarbamate. A solution of (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-benzyl-3-[(4-(benzyloxy)phenyl)sulfonyl](1-ethylpropoxy)amino]-2-25 hydroxypropylcarbamate (222 mg, 0.384 mmol) in 3:1 absolute ethanol : ethyl acetate was combined with Palladium on carbon (10 wt%, 44 mg) and reduced under an atmosphere of Hydrogen gas over 16 hours. The reaction was filtered and evaporated *in vacuo*. The residue was purified on flash grade silica gel eluting with 3:2 ethyl acetate : hexane. Fractions containing the product were combined and

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evaporated *in vacuo*. The residue was triturated with water, filtered and dried under high vacuum to provide (3*R*, 3*aS*, 6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*, 2*R*)-1-benzyl-3-[(1-ethylpropoxy)[(4-hydroxyphenyl)sulfonyl]amino]-2-5 hydroxypropylcarbamate (103 mg, 46%) as a white solid. *H*1-NMR (chloroform-D3): 0.91 (m, 6H), 1.61 (m, 7H), 2.93 (m, 5H), 3.70 (m, 2H), 3.92 (m, 4H), 4.17 (m, 1H), 4.79 (d, 1H), 5.01 (m, 1H), 5.66 (d, 1H), 6.12 (s, 1H), 6.94 (d, 2H), 7.26 (m, 5H), 7.72 (d, 2H). MS(ESI): 601(M+Na).

10

Example 167

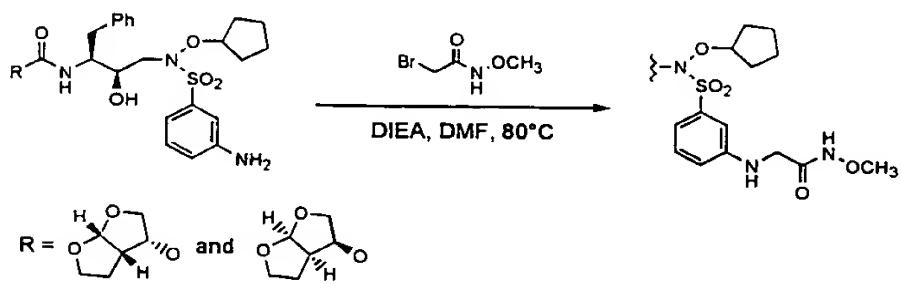


(3*R*, 3*aS*, 6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*, 2*R*)-1-15 benzyl-3-[(cyclopentyloxy)[3-[(2-[methylamino]-2-oxoethylamino)carbonylamino]ethylamino]phenyl]sulfonylamino)-2-hydroxypropylcarbamate and (3*S*, 3*aR*, 6*aS*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*, 2*R*)-1-20 benzyl-3-[(cyclopentyloxy)[3-[(2-[methylamino]-2-oxoethylamino)carbonylamino]ethylamino]phenyl]sulfonylamino)-2-hydroxypropylcarbamate. A solution of 30 mg (0.048 mmol) of a 1:1 mixture of (3*R*, 3*aS*, 6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*, 2*R*)-3-[(3-[(2-aminoethyl)amino]phenylsulfonyl)(cyclopentyloxy)amino]-1-25 benzyl-2-hydroxypropylcarbamate and (3*S*, 3*aR*, 6*aS*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*, 2*R*)-3-[(3-

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[(2-aminoethyl)amino]phenylsulfonyl) (cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate in 2 mL of anhydrous THF was treated with 6.0  $\mu$ L (0.05 mmol) of ethyl isocyanatoacetate. After stirring at RT for 2.5 hours the 5 solution was concentrated *in vacuo*. The residue was dissolved in 3 mL of 2M NH<sub>3</sub>/MeOH and the solution stirred at RT. After 18 hours the solution was concentrated to dryness and the residue subjected to flash chromatography (silica 10 gel, 9:1 CH<sub>2</sub>Cl<sub>2</sub>/2M NH<sub>3</sub> in MeOH) to afford 23 mg (66%) of the desired product as a white foam. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.38-7.07 (10H), 6.88 (2H), 6.39 (1H), 6.16-5.88 (2H), 5.68 (1H), 5.09 (1H), 4.84 (1H), 4.17-2.59 (20H), 2.10-1.25 (10H). MS(ESI): 733 (M+H).

15

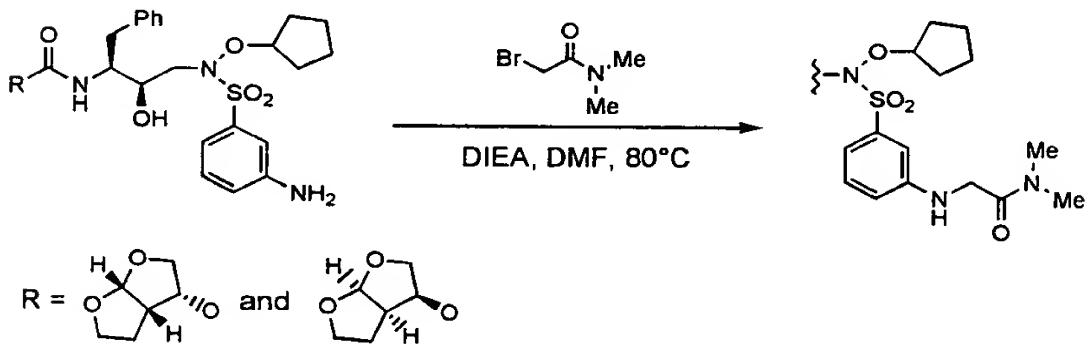
Example 168

(3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-benzyl-3-((cyclopentyloxy)[3-(2-[methoxyamino]-2-oxoethylamino)phenyl]sulfonylamino)-2-hydroxypropyl]carbamate and (3*S*,3a*R*,6a*S*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-benzyl-3-((cyclopentyloxy)[3-(2-[methoxyamino]-2-oxoethylamino)phenyl]sulfonylamino)-2-hydroxypropyl]carbamate. A solution of 0.100 g (0.174 mmol) 20 of a 1:1 mixture of (3*R*,3a*S*,6a*R*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-(1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(3-

- 307 -

aminophenyl)sulfonyl]amino-2-hydroxypropyl)carbamate and (3*S*,3a*R*,6a*S*)hexahydrofuro[2,3-b]furan-3-yl *N*-(*(1S,2R)*-1-benzyl-3-(cyclopentyloxy)[(3-aminophenyl)sulfonyl]amino-2-hydroxypropyl)carbamate (see example 31), 44 mg (0.26 mmol) 5 of *N*-methoxybromoacetamide (prepared in a manner analogous to *N*-methoxy-*N*-methylbromoacetamide, example 88), and 0.045 mL (0.26 mmol) of *N,N*-diisopropylethylamine in 5 mL of anhydrous DMF was heated to 80°C with stirring in a sealed tube. The reaction progress was monitored by HPLC (C18, 10  $H_2O/MeCN/0.1\%TFA$ ). In order to push the reaction further toward completion, additional 1.5 equivalent portions of *N*-methoxybromoacetamide and *N,N*-diisopropylethylamine were added after 4 hours and 3 days. After a total reaction time of 4 days the solution was cooled to RT and concentrated in 15 *vacuo*. The residue was subjected to flash chromatography (SiO<sub>2</sub>, 93:7 CH<sub>2</sub>Cl<sub>2</sub>/2M NH<sub>3</sub> in MeOH) to afford 16 mg (14%) of the desired product as a white foam. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.36-7.00 (9H), 6.85 (2H), 5.60 (1H), 5.20-4.82 (2H), 4.75(2H), 4.10-3.43 (10H), 3.21-2.45 (6H), 1.90-1.39 (10H). MS (ESI): 20 663 (M+H).

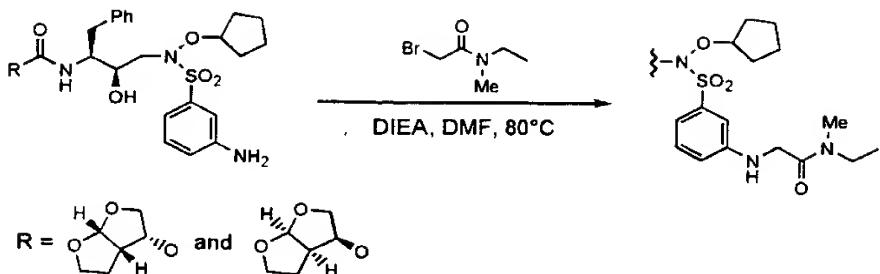
Example 169



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(3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-benzyl-3-((cyclopentyloxy)[3-(2-[dimethylamino]-2-oxoethylamino)phenyl]sulfonylamino)-2-hydroxypropyl]carbamate and (3*S*,3*aR*,6*aS*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-benzyl-3-((cyclopentyloxy)[3-(2-[dimethylamino]-2-oxoethylamino)phenyl]sulfonylamino)-2-hydroxypropyl]carbamate. A solution of 0.100 g (0.174 mmol) of a 1:1 mixture of (3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(3-aminophenyl)sulfonyl]amino-2-hydroxypropyl]carbamate and (3*S*,3*aR*,6*aS*)hexahydrofuro[2,3-*b*]furan-3-yl *N*-[(1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(3-aminophenyl)sulfonyl]amino-2-hydroxypropyl]carbamate (see example 31), 32 mg (0.19 mmol) of *N,N*-dimethylbromoacetamide (prepared in a manner analogous to *N*-methoxy-*N*-methylbromoacetamide, example 88), and 0.033 mL (0.19 mmol) of *N,N*-diisopropylethylamine in 3 mL of anhydrous DMF was heated to 80°C with stirring in a sealed tube. The reaction progress was monitored by HPLC (C18, H<sub>2</sub>O/MeCN/0.1%TFA). In order to push the reaction further toward completion, additional 1.1 equivalent portions of *N,N*-dimethylbromoacetamide and *N,N*-diisopropylethylamine were added after 18 hours and 42 hours. After a total reaction time of 3 days the solution was cooled to RT and concentrated *in vacuo*. The residue was dissolved in EtOAc and the solution washed with aqueous brine (3x), dried over MgSO<sub>4</sub>, and concentrated. The crude product was purified by flash chromatography (SiO<sub>2</sub>, EtOAc) to afford 53 mg (46%) of the desired product as a light yellow foam. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.32-7.14 (8H), 7.10 (1H), 6.93 (1H), 6.86 (1H), 5.61 (1H), 4.96 (1H), 4.91-4.77 (2H), 3.92-3.55 (7H), 3.23-2.77 (12H), 1.86-1.38 (10H). MS (ESI): 661 (M+H).

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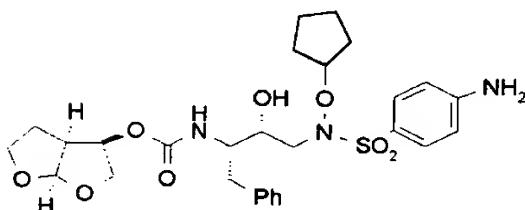
Example 170

5    **(3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl N-[(1S,2R)-1-**  
**benzyl-3-((cyclopentyloxy)[3-(2-[ethyl(methyl)amino]-2-**  
**oxoethylamino)phenyl]sulfonylamino)-2-**  
**hydroxypropyl]carbamate and (3S,3aR,6aS)hexahydrofuro[2,3-**  
**b]furan-3-yl N-[(1S,2R)-1-benzyl-3-((cyclopentyloxy)[3-(2-**  
10   **[ethyl(methyl)amino]-2-oxoethylamino)phenyl]sulfonylamino)-**  
**2-hydroxypropyl]carbamate.** A solution of 0.100 g (0.174  
mmol) of a 1:1 mixture of **(3R,3aS,6aR)hexahydrofuro[2,3-**  
**b]furan-3-yl N-((1S,2R)-1-benzyl-3-(cyclopentyloxy)[(3-**  
**aminophenyl)sulfonyl]amino-2-hydroxypropyl)carbamate and**  
15   **(3S,3aR,6aS)hexahydrofuro[2,3-b]furan-3-yl N-((1S,2R)-1-**  
**benzyl-3-(cyclopentyloxy)[(3-aminophenyl)sulfonyl]amino-2-**  
**hydroxypropyl]carbamate (see example 31), 34 mg (0.19 mmol)**  
of *N*-ethyl-*N*-methylacetamide (prepared in a manner analogous  
to *N*-methoxy-*N*-methylbromoacetamide, example 88), and 0.033  
20   mL (0.19 mmol) of *N,N*-diisopropylethylamine in 3 mL of  
anhydrous DMF was heated to 80°C with stirring in a sealed  
tube. The reaction progress was monitored by HPLC (C18,  
H<sub>2</sub>O/MeCN/0.1%TFA). In order to push the reaction further  
toward completion, additional 1.1 equivalent portions of *N*-  
25   ethyl-*N*-methylacetamide and *N,N*-diisopropylethylamine were  
added after 18 hours and 42 hours. After a total reaction  
time of 3 days the solution was cooled to RT and

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concentrated *in vacuo*. The residue was dissolved in EtOAc and the solution washed with aqueous brine (3x), dried over MgSO<sub>4</sub>, and concentrated. The crude product was purified by flash chromatography (SiO<sub>2</sub>, EtOAc) to afford 61 mg (52%) of  
5 the desired product as a light yellow foam. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): 7.32-7.14 (8H), 7.09 (1H), 6.91 (1H), 6.85 (1H), 5.62 (1H), 5.01-4.77 (3H), 3.95-3.53 (7H), 3.48 (1H), 3.34 (1H), 3.23-2.75 (9H), 1.88-1.41 (10H), 1.27-1.08 (3H). MS (ESI): 675 (M+H).  
10

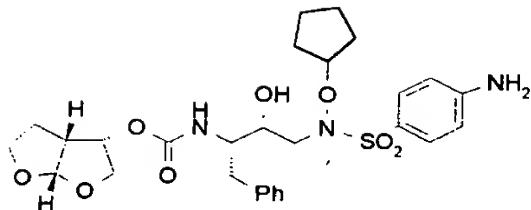
Example 171



15 (3R,3aS,6aR) hexahydrofuro [2,3-b]furan-3-yl N-(1S,2R)-3-[(4-aminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropyl carbamate. This material was obtained in an analogous manner to Example 77, but p-nitrobenzenesulfonyl chloride was used instead of meta nitrobenzenesulfonyl  
20 chloride.

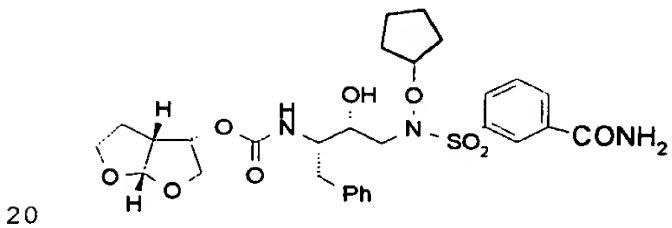
MS: 598 (M+Na), NMR (chloroform-d): 1.2-2.0 (m), 2.75-3.2 (m), 3.6 (dd), 3.7-4.0 (m), 4.2 (s), 4.75 (m), 4.85 (m), 5.0 (m), 5.62 (d), 6.65 (d), 7.2-7.3 (m), 7.55 (d).

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Example 172

5 (3S,3aR,6aS) hexahydrofuro [2,3-b]furan-3-yl N-(1S,2R)-3-  
 [[(4-aminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-  
 hydroxypropyl carbamate. This material was obtained in an  
 analogous manner to Example 77, but p-nitrobenzenesulfonyl  
 chloride was used instead of meta nitrobenzenesulfonyl  
 10 chloride and the starting scaffold was that used in Example  
 39 (opposite stereochemistry at the furanylfuran ring  
 system).

MS: 598 (M+Na). ), NMR (chloroform-d): 1.2-2.0 (m), 2.75-3.2  
 15 (m), 3.6 (dd), 3.7-4.0 (m), 4.2 (s), 4.75 (m), 4.95 (m), 5.1  
 (m), 5.8 (d), 6.65 (d), 7.2-7.3 (m), 7.55 (d).

Example 173

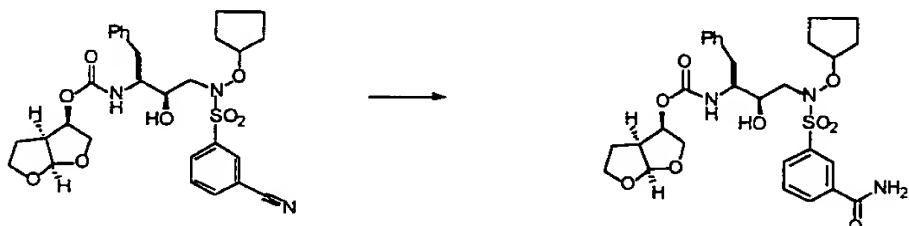
20

Step 1:

(3R,3aS,6aR) hexahydrofuro [2,3-b]furan-3-yl N-(1S,2R)-3-  
 [[(3-cyanophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-

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**hydroxypropyl carbamate.** In a dried flask was introduced 1 eq. of (3*R*, 3*aS*, 6*aR*) Hexahydrofuro[2,3-*b*]furan-3-yl-N-(1*S*, 2*R*)-1-benzyl-3-[(cyclopentyloxy) amino]-2-hydroxypropylcarbamate (53.6 mg, 0.127 mmol) in 2 mL of dried pyridine. To this 5 solution was added 1.2 eq. of the *m*-cyanophenyl sulfonyl chloride (31 mg, 0.153 mmol). This was followed by the addition of catalytic DMAP (1 mg). The reaction was continued at room temperature for 24 h. The solvent was evaporated in vacuo to an oil who was solubilized in ethyl 10 acetate and then washed with 1N hydrochloric acid, and brine. The organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated in vacuo to a residue. The crude material was purified on flash grade silica gel 15 eluting with 50% ethyl acetate in hexane. Fractions containing the product were combined, evaporated in vacuo and dried under high vacuum to provide (3*R*, 3*aS*, 6*aR*) Hexahydrofuro[2,3-*b*]furan-3-yl-N-(1*S*, 2*R*)-1-benzyl-3-[(cyclopentyloxy) [(*m*-cyanophenyl)sulfonyl]amino]-2-hydroxypropyl carbamate (31 mg, 42%). HPLC showed the 20 material to be 98% pure; Ret. time = 12.1 min, tlc in 50% ethyl acetate/ Hexanes indicated an R<sub>f</sub> of 0.3 and LCMS (ES<sup>+</sup>), M+H = 586.3 (M+H).



Step 2:

25 (3*R*, 3*aS*, 6*aR*) hexahydrofuro [2,3-*b*]furan-3-yl N-(1*S*, 2*R*)-3-[(3-carbamoylphenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropyl carbamate. In a flask was introduced 1 eq. (3*R*, 3*aS*, 6*aR*) Hexahydrofuro[2,3-*b*]furan-3-yl-N-(1*S*, 2*R*)-1-

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benzyl-3-[(cyclopentyloxy)[(m-cyanophenyl)sulfonyl]amino-2-hydroxypropyl carbamate (28 mg, 0.048 mmol) in 1 mL acetone. To this solution was added: lurea hydroperoxide (4EQ., 18 mg, 0.19 mmol), K<sub>2</sub>CO<sub>3</sub> (0.1 EQ., 0.7 mg), and the 1 5 mL H<sub>2</sub>O. The reaction was continued at room temperature for 5 h. The solvent was evaporated in vacuo to an oil who was solubilized in ethyl acetate and then washed with and brine. The 10 organic layer was dried over anhydrous magnesium sulfate, filtered and evaporated in vacuo to a residue. The crude material was purified on flash grade silica gel 15 eluting with ethyl acetate. Fractions containing the product were combined, evaporated in vacuo and dried under high vacuum to provide (3R,3aS,6aR)Hexahydrofuro[2,3b]furan-3-yl-N-(1S,2R)-1-benzyl-3-[(cyclopentyloxy)[(m-phenyl-carboxamide)sulfonyl]amino-2-hydroxypropyl carbamate (20.2 mg). HPLC showed the material to be 98% pure; Ret. time = 10.68 min, tlc in ethyl acetate indicated an R<sub>f</sub> of 0.5 and LCMS (ES+), M+H = 604.3 (M+H).

20

Example 173Tablet Formulation

25 The following formulations A, B and C are prepared by wet granulation of the ingredients with a solution of povidone, followed by addition of magnesium stearate and compression.

Formulation A

		<u>mg/tablet</u>
	Active Ingredient	250
30	Lactose B.P.	210
	Povidone B.P.	15
	Sodium Starch Glycollate	20
	Magnesium Stearate	5
		500

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Formulation B

		<u>mg/tablet</u>
	Active Ingredient	250
	Lactose B.P.	150
5	Avicel PH 101	60
	Povidone B.P.	15
	Sodium Starch Glycollate	20
	Magnesium Stearate	<u>5</u>
		500

10

Formulation C

		<u>mg/tablet</u>
	Active Ingredient	250
	Lactose B.P.	200
15	Starch	50
	Povidone	5
	Magnesium Stearate	<u>4</u>
		359

20 The following formulations, D and E, are prepared by direct compression of the admixed ingredients. The lactose in formulation E is of the direct compression type (Dairy Crest—"Zeparox").

25 Formulation D

		<u>mg/tablet</u>
	Active Ingredient	250
	Pregelatinized Starch NF15	<u>150</u>
		400

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Formulation E

	<u>mg/tablet</u>
Active Ingredient	250
Lactose B.P.	150
5 Avicel	<u>100</u>
	500

Formulation F (Controlled Release Formulation)

10 The formulation is prepared by wet granulation of the ingredients with a solution of povidone followed by the addition of magnesium stearate and compression.

	<u>mg/tablet</u>
Active Ingredient	500
15 Hydroxypropylmethylcellulose (Methocel K4M Premium)	112
Lactose B.P.	53
Povidone B.P.	28
Magnesium Stearate	<u>7</u>
20	700

Drug release takes place over a period of about 6-8 hours and is complete after 12 hours.

25

Example 174

Capsule Formulations

Formulation A

A capsule formulation is prepared by admixing the ingredients of formulation D in Example 134 above and 30 filling into a two-part hard gelatin capsule. Formulation B (infra) is prepared in a similar manner.

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Formulation B

	<u>mg/capsule</u>
Active Ingredient	250
Lactose B.P.	143
5 Sodium Starch Glycollate	25
Magnesium Stearate	<u>2</u>
	420

Formulation C

	<u>mg/capsule</u>
Active Ingredient	250
Macrogel 4000 B.P.	<u>350</u>
	600

15 Capsules of formulation C are prepared by melting the Macrogel 4000 B.P., dispersing the active ingredient in the melt and filling the melt into a two-part hard gelatin capsule.

Formulation D

	<u>mg/capsule</u>
Active Ingredient	250
Lecithin	100
Arachis Oil	<u>100</u>
	450

25 Capsules of formulation D are prepared by dispersing the active ingredient in the lecithin and arachis oil and filling the dispersion into soft, elastic gelatin capsules.

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Formulation E

		<u>mg/capsule</u>
	Active Ingredient	150.0
	Vitamin E TPGS	400.0
5	Polyethylene Glycol 400 NF	200.5
	Propylene Glycol USP	39.5

Four (4) kilograms (kg) of Vitamin E TPGS (obtained from Eastman Chemical Co.) was heated at 50°C until liquefied.

10 To the liquified Vitamin E TPGS, 2.005 kg of polyethylene glycol 400 (PEG400) (low aldehyde, <10 ppm, obtained from Union Carbide or Dow Chemical Co.) heated to 50°C was added and mixed until a homogeneous solution was formed. The resultant solution was heated to 65°C. 1.5 kg of active 15 ingredient was dissolved in the liquefied solution of Vitamin E TPGS and PEG 400. 0.395 kg of propylene glycol at room temperature was added and mixed until a homogenous solution was formed. The solution was cooled to 28-35°C. The solution was then de-gassed. The mixture was preferably 20 encapsulated at 28-35°C at a fill weight equivalent to 150 mg of volatiles-free compound, into Size 12 oblong, white opaque soft gelatin capsules using a capsule filling machine. The capsule shells were dried to a constant fill moisture of 3-6% water and a shell hardness of 7-10 newtons, 25 and placed in a suitable container.

Formulation F (Controlled Release Capsule)

30 The following controlled release capsule formulation is prepared by extruding ingredients a,b, and c using an extruder, followed by spheronization of the extrudate and drying. The dried pellets are then coated with release-controlling membrane (d) and filled into a two-piece, hard gelatin capsule.

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		<u>mg/capsule</u>
	(a) Active Ingredient	250
	(b) Microcrystalline Cellulose	125
5	(c) Lactose B.P.	125
	(d) Ethyl Cellulose	13
		513

10

Example 175Injectable FormulationFormulation A

	Active Ingredient	200 mg
15	Hydro chloric Acid Solution 0.1M or	
	Sodium Hydroxide Solution 0.1M q.s. to pH	4.0 to 7.0
	Sterile water q.s. to	10 ml

20 The active ingredient is dissolved in most of the water (35° - 40° C) and the pH adjusted to between 4.0 and 7.0 with the hydrochloric acid or the sodium hydroxide as appropriate. The batch is then made up to volume with water and filtered through a sterile micropore filter into a sterile 10 ml amber glass vial (type 1) and sealed with sterile closures  
25 and overseals.

Formulation B

	Active Ingredient	125 mg
30	Sterile, Pyrogen-free, pH 7 Phosphate Buffer, q.s. to 25 ml	

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Example 176

Intramuscular Injection

	Active Ingredient	200 mg
5	Benzyl Alcohol	0.10 g
	Glycofurool 75	1.45 g
	Water for injection q.s. to	3.00 ml

10 The active ingredient is dissolved in the glycofurool. The benzyl alcohol is then added and dissolved, and water added to 3 ml. The mixture is then filtered through a sterile micropore filter and sealed in sterile 3 ml amber glass vials (type 1).

15

Example 177

Syrup Formulation

	Active Ingredient	250 mg
	Sorbitol Solution	1.50 g
20	Glycerol	2.00 g
	Sodium Benzoate	0.005 g
	Flavor, Peach 17.42.3169	0.0125 ml
	Purified Water q.s. to	5.00 ml

25 The active ingredient is dissolved in a mixture of the glycerol and most of the purified water. An aqueous solution of the sodium benzoate is then added to the solution, followed by addition of the sorbital solution and finally the flavor. The volume is made up with purified water and mixed well.

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Example 178

Suppository Formulation

		<u>mg/capsule suppository</u>
	Active Ingredient	250
5	Hard Fat, B.P. (Witepsol H15-Dynamit Nobel)	1770
		2020

One-fifth of the Witepsol H15 is melted in a steam-jacketed pan at 45°C maximum. The active ingredient is sifted through a 200µm sieve and added to the molten base 10 with mixing, using a Silverson fitted with a cutting head, until a smooth dispersion is achieved. Maintaining the mixture at 45° C, the remaining Witepsol H15 is added to the suspension and stirred to ensure a homogenous mix. The 15 entire suspension is passed through a 250µm stainless steel screen and, with continuous stirring, is allowed to cool to 45°C. At a temperature of 38°C to 40° C, 2.02 g of the mixture is filled into suitable, 2 ml plastic molds. The suppositories are allowed to cool to room temperature.

20

Example 179

Pessary Formulation

		<u>mg/pessary</u>
	Active Ingredient	250
	Anhydrate Dextrose	380
25	Potato Starch	363
	Magnesium Stearate	7
		1000

30

The above ingredients are mixed directly to form a pessary.

Example 180

Anti-Viral Activity

35

We measured the enzyme inhibition constants of the

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compounds listed in Table I against HIV-1 protease using the methods of:

Maschera, B., Darby, G., Palú, G., Wright, L. L.,  
Tisdale, M., Myers, R., Blair, E. D. and Furfine, E. S.,  
5 Human Immunodeficiency Virus: Mutations in the Viral  
Protease that Confer Resistance to Saquinavir Increase the  
Dissociation Rate Constant for the Protease-Saquinavir  
Complex, *J. Biol. Chem.*, 271: 33231-33235 (1996); and  
Toth, M. V. and Marshall, G. R. (1990) *Int. J. Peptide*  
10 *Protein Res.* 36, 544-550.

Antiviral activity assay in MT4 cells

Antiviral HIV activity and compound-induced cytotoxicity were measured in parallel by means of a 15 propidium iodide based procedure in the human T-cell lymphotropic virus transformed cell line MT4. Aliquots of the test compounds were serially diluted in medium (RPMI 1640, 10% fetal calf serum (FCS), and gentamycin) in 96-well plates (Costar 3598) using a Cetus Pro/Pette. Exponentially 20 growing MT4 cells were harvested and centrifuged at 1000 rpm for 10 min in a Jouan centrifuge (model CR 4 12). Cell pellets were resuspended in fresh medium (RPMI 1640, 20% FCS, 20% IL-2, and gentamycin) to a density of  $5 \times 10^5$  cells/ml. Cell aliquots were infected by the addition of 25 HIV-1 (strain IIIB) diluted to give a viral multiplicity of infection of  $100 \times \text{TCID}_{50}$ . A similar cell aliquot was diluted with medium to provide a mock-infected control. Cell infection was allowed to proceed for 1 hr at 37°C in a tissue culture incubator with humidified 5% CO<sub>2</sub> atmosphere. 30 After the 1 hr incubation the virus/cell suspensions were diluted 6-fold with fresh medium, and 125 µl of the cell suspension was added to each well of the plate containing prediluted compound. Plates were then placed in a tissue

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culture incubator with humidified 5% CO<sub>2</sub> for 5 days. At the end of the incubation period, 27  $\mu$ l of 5% Nonidet-40 was added to each well of the incubation plate. After thorough mixing with a Costar multitip pipetter, 60  $\mu$ l of the mixture 5 was transferred to filter-bottomed 96-well plates. The plates were analyzed in an automated assay instrument (Screen Machine, Idexx Laboratories). The assay makes use of a propidium iodide dye to estimate the DNA content of each well.

10

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- 15 2. Schwartz, O., et al. 1988. A rapid and simple colorimetric test for the study of anti-HIV agents. *AIDS Res. and Human Retroviruses*, **4**(6):441-447.
- 20 3. Daluge, S.M., et al. 1994. 5-chloro-2'3'-deoxy-3'fluorouridine (935U83), a selective anti-human immuno-deficiency virus agent with an improved metabolic and toxicological profile. *Antimicro. Agents and Chemother.*, **38** (7):1590-1603.

The anti-viral potency of the compounds of Table 1 in MT-4 cells was determined using the above technique. The 25 results are shown in Table 2 as IC<sub>50</sub> values expressed in  $\mu$ M.

In Table 2, the following classifications have been employed:

- "A": K<sub>i</sub> of less than 1 nM;
- "B": K<sub>i</sub> between 1 and 10 nM;
- 30 "C": K<sub>i</sub> between 10 and 100 nM;
- "D": K<sub>i</sub> greater than 100 nM;
- "E": IC<sub>50</sub> of 0.1  $\mu$ M or less;

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"F": IC50 between 0.1 and 0.5  $\mu$ M;

"G": IC50 between 0.5 and 1.0  $\mu$ M;

"H": IC50 greater than 1.0  $\mu$ M.

The designation "NA" is used where a given  
5 compound was not tested.

The designation ">" is used where a given Ki or  
IC50 for a compound is greater than the range given for the  
designated letters.

Table 2

5	<u>Compound</u>	Ki (enzyme) [nM] IC50		<u>Compound</u>	Ki (enzyme) [nM] IC50	
		(MT-4 cells)	[μM]		(MT-4 cells)	[μM]
	1	C H		19	C H	
	2	C H		20	B H	
	3	C H		21	C H	
	4	C H		22	B H	
	5	B G		23	B H	
	6	C H		24	A H	
	7	B H		25	A G	
	8	A G		26	B H	
	9	B >E		27	A G	
	11	B H		28	A F	
	12	>B NA		29	A E	
	13	C NA		30	A F	
	14	A F		31	A E	
	15	B H		32	A E	
	16	C H		33	A E	
	17	C H		34	A F	
	18	B >G		35	A >G	

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36	A E	55	A E
37	A E	56	A F
38	A E	57	A E
39	A F	58	A F
40	A E	59	A E
41	A E	60	A F
42	A NA	61	B G
43	A NA	62	B H
44	A E	63	B NA
45	A E	64	A H
46	A E	65	A F
47	A G	66	A E
48	A F	67	A F
49	A E	68	A E
50	A E	69	A F
51	A F	70	A >F
52	A E	71	A E
53	A E	72	B G
54	A E	73	A E

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74	A E	100	C F
75	A >F	103	A E
76	A F	104	A E
77	A E	105	A E
78	A E	106	A F
79	A F	107	A NA
83	A F	108	C >F
84	A NA	109	C >E
85	A NA	110	A F
86	A E	111	B H
87	A E	112	B H
88	A E	113	A E
89	A NA	114	A E
90	A E	115	D G
91	A NA	116	D G
92	A NA	117	D G
97	A E	118	D G
98	A NA	119	D H
99	A NA		

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120	NA NA	137	A E
121	A F	138	A E
122	A E	139	A E
123	A E	140	A E
124	A E	141	A H
125	A E	142	A F
126	D H	143	A E
127	A E	144	A E
128	D H	145	A E
129	NA NA	146	A E
130	A E	147	A E
131	A E	148	A E
132	A E	149	A E
133	A F	150	A E
134	A E	151	A E
135	B E	152	C G
136	A E	153	A E

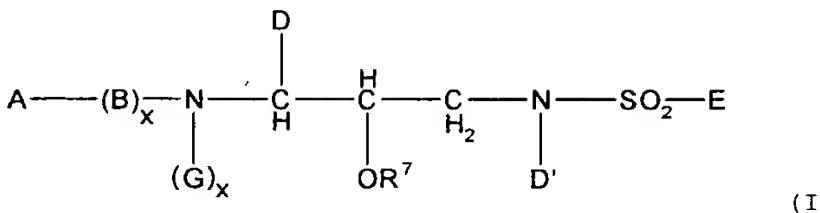
154	A E	164	A E
155	A E	165	NA NA
156	A E	166	A E
157	NA NA	167	A F
158	NA NA	168	A E
159	A E	169	A E
160	A E	170	A E
161	B H	171	A E
162	A E	172	A E
163	A E	173	A E

As demonstrated above, all of the compounds tested displayed inhibitory and anti-viral activity. Moreover, several of these compounds exhibited activity levels far greater than those of known HIV protease inhibitors. While we have described a number of embodiments of this invention, it is apparent that our basic constructions may be altered to provide other embodiments which utilize the products, processes and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims, rather than by the specific embodiments which have been presented by way of example.

Claims

We claim:

1. A compound of formula (I):



5

wherein:

A is selected from H; Ht;  $-R^1$ -Ht;  $-R^1-C_1-C_6$  alkyl, which is optionally substituted with one or more groups independently selected from hydroxy,  $C_1-C_4$  alkoxy, Ht,  $-O-Ht$ ,  $-NR^2-CO-N(R^2)_2$  or  $-CO-N(R^2)_2$ ;  $-R^1-C_2-C_6$  alkenyl, which is optionally substituted with one or more groups independently selected from hydroxy,  $C_1-C_4$  alkoxy, Ht,  $-O-Ht$ ,  $-NR^2-CO-N(R^2)_2$  or  $-CO-N(R^2)_2$ ; or  $R^7$ ;

15 each  $R^1$  is independently selected from  $-C(O)-$ ,  $-S(O)_2-$ ,  $-C(O)-C(O)-$ ,  $-O-C(O)-$ ,  $-O-S(O)_2-$ ,  $-NR^2-S(O)_2-$ ,  $-NR^2-C(O)-$  or  $-NR^2-C(O)-C(O)-$ ;

each Ht is independently selected from  $C_3-C_7$  cycloalkyl;  $C_5-C_7$  cycloalkenyl;  $C_6-C_{10}$  aryl; or a 5-7 membered saturated or unsaturated heterocycle, containing one or more heteroatoms selected from N,  $N(R^2)$ , O, S and  $S(O)_n$ ; wherein said aryl or said heterocycle is optionally fused to Q; and wherein any member of said Ht is optionally substituted with one or more substituents independently selected from oxo,  $-OR^2$ ,  $SR^2$ ,  $-R^2$ ,  $-N(R^2)(R^2)$ ,  $-R^2-OH$ ,  $-CN$ ,  $-CO_2R^2$ ,  $-C(O)-N(R^2)_2$ ,  $-S(O)_2-N(R^2)_2$ ,  $-N(R^2)-C(O)-R^2$ ,  $-C(O)-R^2$ ,  $-S(O)_n-R^2$ ,  $-OCF_3$ ,  $-S(O)_n-Q$ , methylenedioxy,  $-N(R^2)-S(O)_2(R^2)$ , halo,  $-CF_3$ ,  $-NO_2$ , Q,  $-OQ$ ,  $-OR^7$ ,  $-SR^7$ ,  $-R^7$ ,  $-N(R^2)(R^7)$  or  $-N(R^7)_2$ ;

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each  $R^2$  is independently selected from H, Ht or  $C_1$ - $C_6$  alkyl optionally substituted with Q or  $R^{10}$ ;

B, when present, is  $-N(R^2)-C(R^3)_2-C(O)-$ ;

each x is independently 0 or 1;

5 each  $R^3$  is independently selected from H, Ht,  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_3$ - $C_6$  cycloalkyl or  $C_5$ - $C_6$  cycloalkenyl; wherein any member of said  $R^3$ , except H, is optionally substituted with one or more substituents selected from  $-OR^2$ ,  $-C(O)-NH-R^2$ ,  $-S(O)_n-N(R^2)(R^2)$ , Ht,

10  $-CN$ ,  $-SR^2$ ,  $-CO_2R^2$ ,  $NR^2-C(O)-R^2$ ;

each n is independently 1 or 2;

G, when present, is selected from H,  $R^7$  or  $C_1$ - $C_4$  alkyl, or, when G is  $C_1$ - $C_4$  alkyl, G and  $R^7$  are bound to one another either directly or through a  $C_1$ - $C_3$  linker to form a 15 heterocyclic ring; or

when G is not present, the nitrogen to which G is attached is bound directly to the  $R^7$  group in  $-OR^7$  with the concomitant displacement of one  $-ZM$  group from  $R^7$ ;

20 D is selected from Q;  $C_1$ - $C_6$  alkyl or  $C_2$ - $C_4$  alkenyl, which is optionally substituted with one or more groups selected from  $C_3$ - $C_6$  cycloalkyl,  $-OR^2$ ,  $-S-Ht$ ,  $-R^3$ ,  $-O-Q$  or Q;  $C_3$ - $C_6$  cycloalkyl or  $C_5$ - $C_6$  cycloalkenyl, which is optionally substituted with or fused to Q;

25 each Q is independently selected from a 3-7 membered saturated, partially saturated or unsaturated carbocyclic ring system; or a 5-7 membered saturated, partially saturated or unsaturated heterocyclic ring containing one or more heteroatoms selected from O, N, S,  $S(O)_n$  or  $N(R^2)$ ; wherein Q is optionally substituted with one 30 or more groups selected from oxo,  $-OR^2$ ,  $-R^2$ ,  $-N(R^2)_2$ ,  $-N(R^2)-C(O)-R^2$ ,  $-R^2-OH$ ,  $-CN$ ,  $-CO_2R^2$ ,  $-C(O)-N(R^2)_2$ , halo or  $-CF_3$ ;

D' is selected from  $-OR^{10}$ ,  $-N=R^{10}$  or  $-N(R^{10})-R^1-R^3$ ;

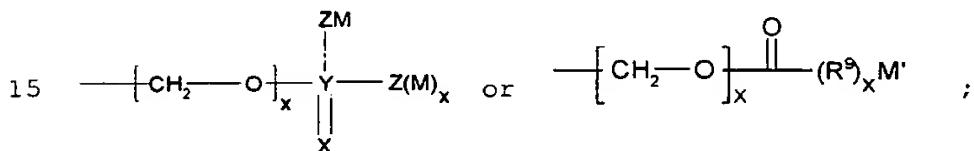
E is selected from Ht; O-Ht; Ht-Ht;  $-O-R^3$ ;

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-N(R<sup>2</sup>)(R<sup>3</sup>); C<sub>1</sub>-C<sub>6</sub> alkyl, which is optionally substituted with one or more groups selected from R<sup>4</sup> or Ht; C<sub>2</sub>-C<sub>6</sub> alkenyl, which is optionally substituted with one or more groups selected from R<sup>4</sup> or Ht; C<sub>3</sub>-C<sub>6</sub> saturated carbocycle, which is 5 optionally substituted with one or more groups selected from R<sup>4</sup> or Ht; or C<sub>5</sub>-C<sub>6</sub> unsaturated carbocycle, which is optionally substituted with one or more groups selected from R<sup>4</sup> or Ht;

each R<sup>4</sup> is independently selected from -OR<sup>2</sup>,  
10 -SR<sup>2</sup>, -C(O)-NHR<sup>2</sup>, -S(O)<sub>2</sub>-NHR<sup>2</sup>, halo, -NR<sup>2</sup>-C(O)-R<sup>2</sup>, -N(R<sup>2</sup>)<sub>2</sub> or -CN;

each R<sup>7</sup> is independently selected from hydrogen,



wherein each M is independently selected from H, Li, Na, K, Mg, Ca, Ba, -N(R<sup>2</sup>)<sub>4</sub>, C<sub>1</sub>-C<sub>12</sub>-alkyl, C<sub>2</sub>-C<sub>12</sub>-alkenyl, or -R<sup>6</sup>; wherein 1 to 4 -CH<sub>2</sub> radicals of the alkyl 20 or alkenyl group, other than the -CH<sub>2</sub> that is bound to Z, is optionally replaced by a heteroatom group selected from O, S, S(O), S(O<sub>2</sub>), or N(R<sup>2</sup>); and wherein any hydrogen in said alkyl, alkenyl or R<sup>6</sup> is optionally replaced with a substituent selected from oxo, -OR<sup>2</sup>, -R<sup>2</sup>, N(R<sup>2</sup>)<sub>2</sub>, N(R<sup>2</sup>)<sub>3</sub>, 25 R<sup>2</sup>OH, -CN, -CO<sub>2</sub>R<sup>2</sup>, -C(O)-N(R<sup>2</sup>)<sub>2</sub>, S(O)<sub>2</sub>-N(R<sup>2</sup>)<sub>2</sub>, N(R<sup>2</sup>)-C(O)-R<sub>2</sub>, C(O)R<sup>2</sup>, -S(O)<sub>n</sub>-R<sup>2</sup>, OCF<sub>3</sub>, -S(O)<sub>n</sub>-R<sup>6</sup>, N(R<sup>2</sup>)-S(O)<sub>2</sub>(R<sup>2</sup>), halo, -CF<sub>3</sub>, or -NO<sub>2</sub>;

M' is H, C<sub>1</sub>-C<sub>12</sub>-alkyl, C<sub>2</sub>-C<sub>12</sub>-alkenyl, or -R<sup>6</sup>; wherein 1 to 4 -CH<sub>2</sub> radicals of the alkyl or alkenyl group 30 is optionally replaced by a heteroatom group selected from O, S, S(O), S(O<sub>2</sub>), or N(R<sup>2</sup>); and wherein any hydrogen in said alkyl, alkenyl or R<sup>6</sup> is optionally replaced with a substituent selected from oxo, -OR<sup>2</sup>, -R<sup>2</sup>, -N(R<sup>2</sup>)<sub>2</sub>, N(R<sup>2</sup>)<sub>3</sub>, -R<sup>2</sup>OH, -CN, -CO<sub>2</sub>R<sup>2</sup>, -C(O)-N(R<sup>2</sup>)<sub>2</sub>, -S(O)<sub>2</sub>-N(R<sup>2</sup>)<sub>2</sub>,

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$-N(R^2)-C(O)-R_2$ ,  $-C(O)R^2$ ,  $-S(O)_n-R^2$ ,  $-OCF_3$ ,  $-S(O)_n-R^6$ ,  
 $-N(R^2)-S(O)_2(R^2)$ , halo,  $-CF_3$ , or  $-NO_2$ ;

Z is O, S,  $N(R^2)_2$ , or, when M is not present, H.

Y is P or S;

5 X is O or S;

$R^9$  is  $C(R^2)_2$ , O or  $N(R^2)$ ; and wherein when Y is S,  
Z is not S;

10  $R^6$  is a 5-6 membered saturated, partially  
saturated or unsaturated carbocyclic or heterocyclic ring  
system, or an 8-10 membered saturated, partially saturated  
or unsaturated bicyclic ring system; wherein any of said  
heterocyclic ring systems contains one or more heteroatoms  
selected from O, N, S,  $S(O)_n$  or  $N(R^2)$ ; and wherein any of  
15 said ring systems optionally contains 1 to 4 substituents  
independently selected from OH,  $C_1-C_4$  alkyl,  $O-C_1-C_4$  alkyl or  
 $O-C(O)-C_1-C_4$  alkyl;

$R^8$  is selected from  $C_1-C_8$  alkyl,  $C_3-C_7$  alkyl or  
cyano substituted  $C_2-C_6$  alkenyl; and

20  $R^{10}$  is selected from  $C_1-C_8$  alkyl,  $C_2-C_6$  alkenyl,  $C_6-C_{14}$   
aryl or Ht, wherein  $R^{10}$  optionally contains up to three  
substituents independently selected from  $-R^3$ ,  $-CN$ ,  $-SR^5$ ,  
 $-SOR^5$ ,  $-SO_2R^5$ ,  $-SR-NR^5-C(O)R^6$ ,  $-NR^5-(SO_2)R^5$ ,  $-C(O)N(R^5)_2$ ,  
 $-C(S)N(R^5)_2$ ,  $-S(O)_2N(R^5)_2$ ,  $-C(O)R^6$ ,  $-C(S)R^6$ ,  $-N(R^5)_2$ ,  $-NR^5-$   
 $C(O)R^5$ ,  $-NR^5-C(O)OR^5$ ,  $-NR^5-C(O)N(R^5)_2$ ,  $-NR^5-C(S)R^5$ ,  $-NR^5-$   
25  $C(S)OR^5$ ,  $-NR^5-C(S)N(R^5)_2$ ,  $-NR^5-C[=N(R^5)]-N(R^5)_2$ ,  $-NH-C[=N-NO_2]-$   
 $NH_2$ ,  $-NH-C[=N-NO_2]-OR^5$ ,  $-N(R^8)_2-C(O)R^8$ ,  $-NH-C[=N-NO_2]-NH_2$ ,  $-NH-$   
 $C[=N-NO_2]-OR^5$ ,  $-N(R^8)_2-C(O)R^6$ ,  $-OC(O)R^6$ ,  $-OC(O)N(R^5)_2$ ,  
 $-OC(S)N(R^5)_2$ , wherein any one of the  $-CH_2$  groups of said  
alkyl or alkenyl chains of  $R^{10}$  may be optionally replaced by  
30 O, S, SO,  $SO_2$ ,  $C(O)$  or  $NR^5$ ;

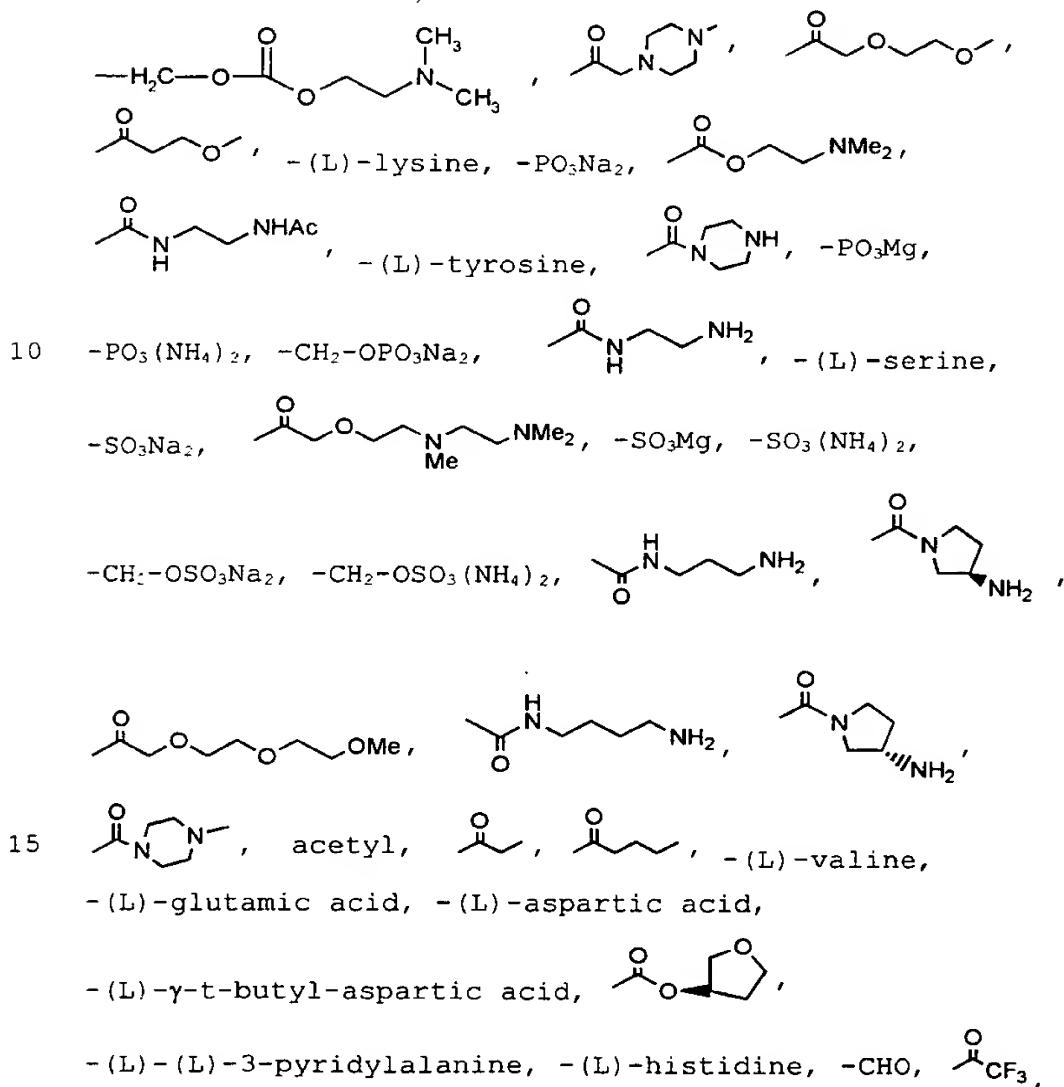
wherein each  $R^5$  is independently selected from  
hydrogen,  $C_1-C_8$  alkyl,  $C_2-C_8$  alkenyl,  $C_2-C_8$  alkynyl or Ht,  
wherein each  $R^5$ , except for hydrogen, is optionally  
substituted with  $-CF_3$ ,  $-PO_3R^3$ , azido or halo;

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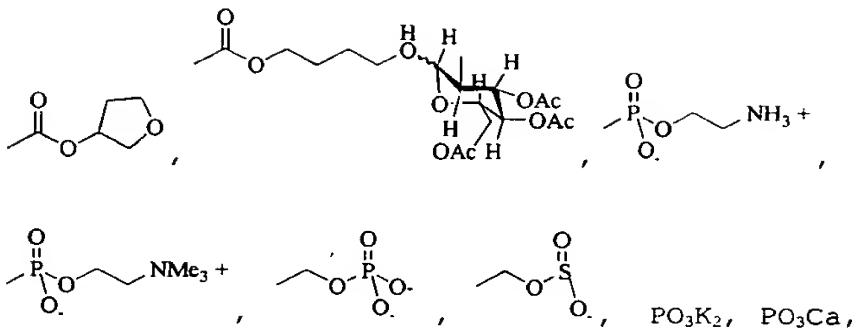
or a pharmaceutically acceptable derivative thereof.

2. The compound according to claim 1, wherein at least one R<sup>7</sup> is selected from:

5



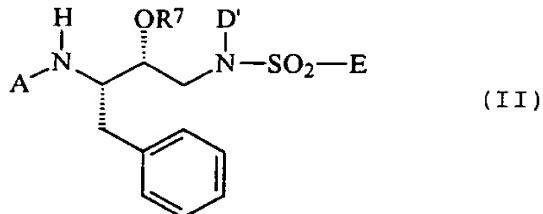
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5 PO<sub>3</sub>-spermine, PO<sub>3</sub>-(spermidine)<sub>2</sub> or PO<sub>3</sub>-(meglamine)<sub>2</sub>.

3. A compound of formula (II):

10



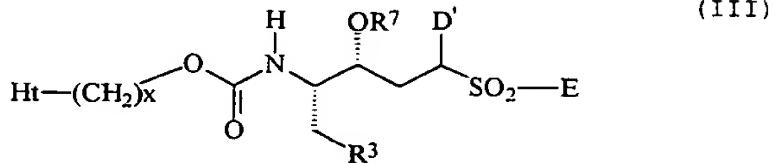
15

wherein A, R<sup>7</sup>, D' and E are as defined in claim 1;  
or a pharmaceutically acceptable derivative thereof.

20

4. A compound of formula (III):

25

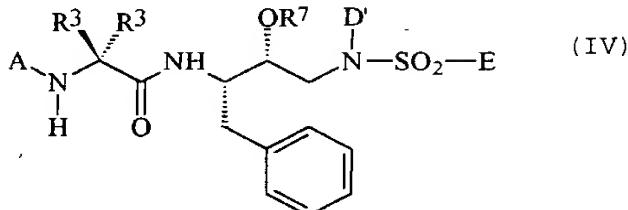


wherein Ht, x, R<sup>3</sup>, R<sup>7</sup>, D' and E are as defined in claim 1;  
or a pharmaceutically acceptable derivative thereof.

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## 5. A compound of formula (IV):

5



wherein A, R<sup>3</sup>, R<sup>7</sup>, D' and E are as defined in claim 1;  
 10 or a pharmaceutically acceptable derivative thereof.

## 6. The compound according to claim 3, wherein:

A is -C(O)Ht;

D' is -O-R<sup>10</sup>;

15 E is C<sub>6</sub>-C<sub>10</sub> aryl optionally substituted with one or more substituents selected from oxo, -OR<sup>2</sup>, SR<sup>2</sup>, -R<sup>2</sup>, -N(R<sup>2</sup>)<sub>2</sub>, -R<sup>2</sup>-OH, -CN, -CO<sub>2</sub>R<sup>2</sup>, -C(O)-N(R<sup>2</sup>)<sub>2</sub>, -S(O)<sub>2</sub>-N(R<sup>2</sup>)<sub>2</sub>, -N(R<sup>2</sup>)-C(O)-R<sup>2</sup>, -C(O)-R<sup>2</sup>, -S(O)<sub>n</sub>-R<sup>2</sup>, -OCF<sub>3</sub>, -S(O)<sub>n</sub>-Q, methylenedioxy, -N(R<sup>2</sup>)-S(O)<sub>2</sub>(R<sup>2</sup>), halo, -CF<sub>3</sub>, -NO<sub>2</sub>, Q, -OQ, -OR<sup>7</sup>, -SR<sup>7</sup>, -R<sup>7</sup>,  
 20 -N(R<sup>2</sup>)(R<sup>7</sup>) or -N(R<sup>7</sup>)<sub>2</sub>; or a 5-membered heterocyclic ring containing one S and optionally containing N as an additional heteroatom, wherein said heterocyclic ring is optionally substituted with one to two groups independently selected from -CH<sub>3</sub>, R<sup>4</sup>, or Ht.

25

## 7. The compound according to claim 3, wherein:

E is a 5-membered heterocyclic ring containing one S and optionally containing N as an additional heteroatom, wherein said heterocyclic ring is optionally substituted  
 30 with one to two groups independently selected from -CH<sub>3</sub>, R<sup>4</sup>, or Ht.

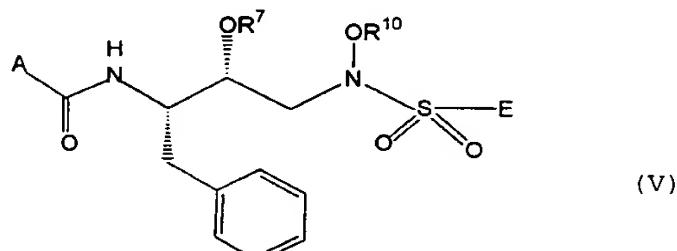
## 8. The compound according to claim 3, wherein:

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R<sup>7</sup> in -OR<sup>7</sup> group shown in formula II is -PO(OM)<sub>2</sub> or C(O)CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> and both R<sup>7</sup> in -N(R<sup>7</sup>)<sub>2</sub> are H; or R<sup>7</sup> in -OR<sup>7</sup> group shown in formula II is C(O)CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, one R<sup>7</sup> in -N(R<sup>7</sup>)<sub>2</sub> is C(O)CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> and the other is H; and  
5 wherein M is H, Li, Na, K or C<sub>1</sub>-C<sub>4</sub> alkyl.

9. A compound according to claim 1, having formula (V):

10

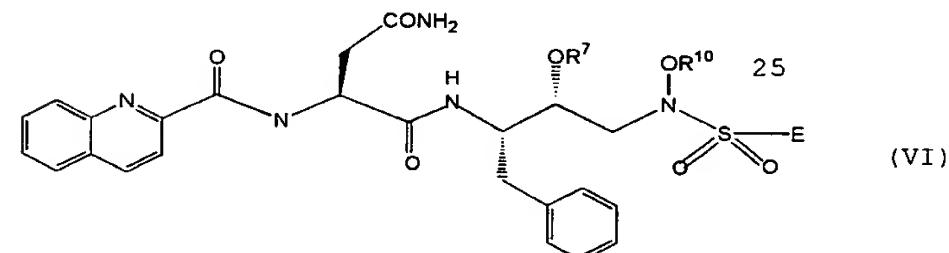


15

wherein A, R<sup>7</sup>, R<sup>10</sup> and E are as defined in claim 1;  
20 or a pharmaceutically acceptable derivative thereof.

10. A compound of formula (VI):

30



wherein:

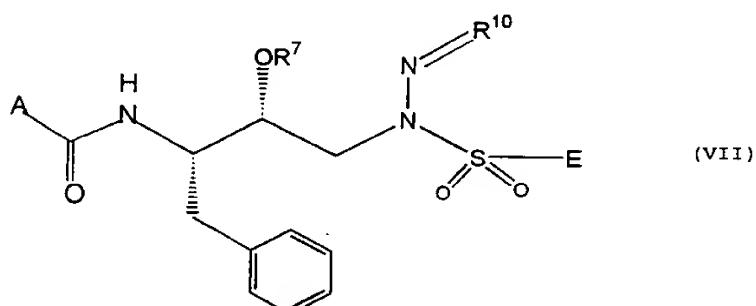
R<sup>10</sup> and R<sup>7</sup> are as defined in claim 1;

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E is  $C_6$ - $C_{14}$  aryl, optionally substituted with one or more groups selected from the group consisting of nitro, oxo, alkoxy, amino, hydroxyamino; heterocyclyl, optionally substituted with one or more groups selected from the group consisting of nitro, oxo, alkoxy, amino, hydroxyamino or  $N(CO)OCH_3$ ;

5 or a pharmaceutically acceptable derivative thereof.

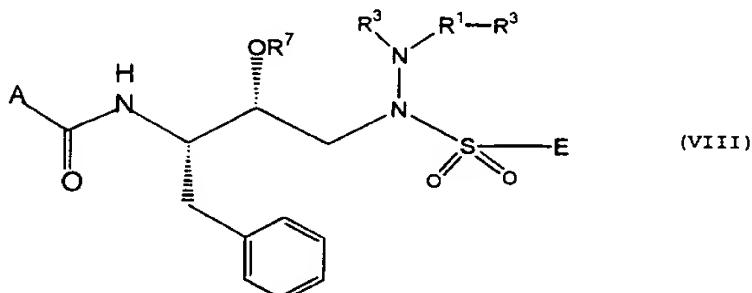
## 10 11. A compound of formula (VII):



wherein A, E,  $R^7$  and  $R^{10}$  are as defined in claim 1;  
or a pharmaceutically acceptable derivative thereof.

15

## 12. A compound of formula (VIII):



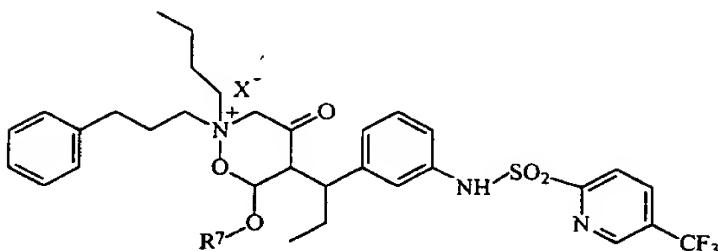
wherein A,  $R^1$ ,  $R^3$ ,  $R^7$  and E are as defined in claim 1;

or a pharmaceutically acceptable salt thereof.

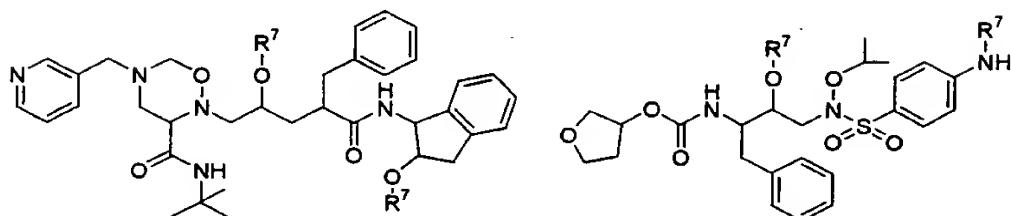
13. A compound selected from:

5

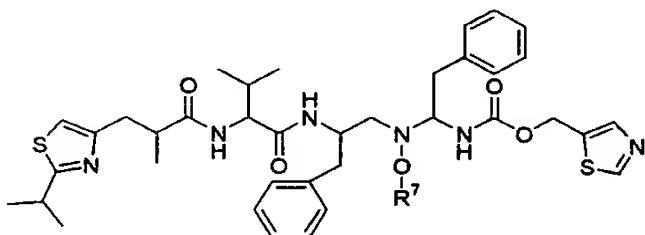
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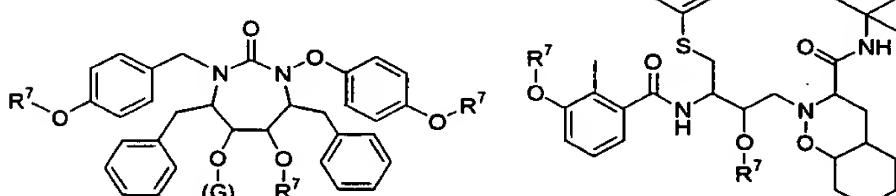
15

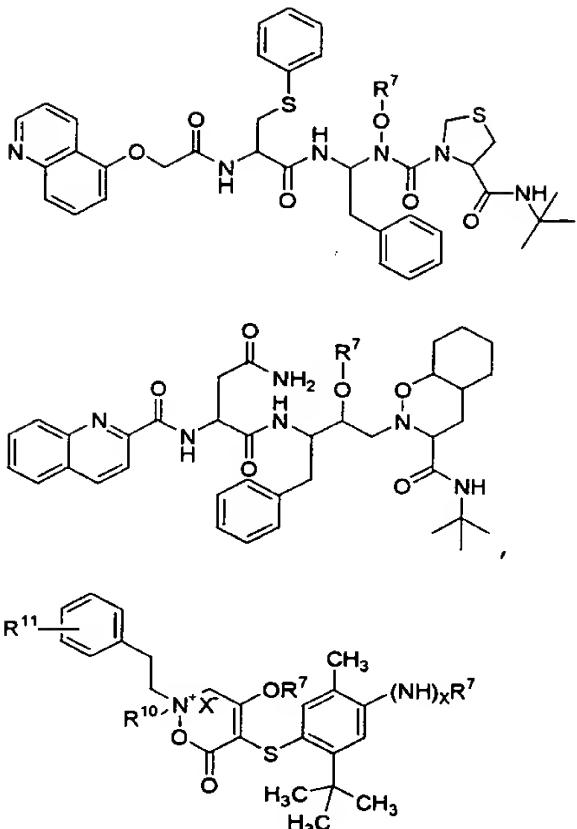


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25





wherein  $R^{10}$  is selected from isopropyl or cyclopentyl;  $R^{11}$  is selected from  $NHR^7$  or  $OR^7$ ;  $x$ ,  $R^7$  and  $G$  are as defined in claim 1; and  $X^-$  is a pharmaceutically acceptable counterion.

14. A compound selected from:

(3*R*,3*aS*,6*aR*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(3-[2-(dimethylamino)ethyl]aminophenyl)sulfonyl]amino-2-hydroxypropyl)carbamate;

(3*S*,3*aR*,6*aS*) hexahydrofuro[2,3-*b*]furan-3-yl *N*-((1*S*,2*R*)-1-benzyl-3-(cyclopentyloxy)[(3-[2-(dimethylamino)ethyl]aminophenyl)sulfonyl]amino-2-hydroxypropyl)carbamate;

(3*R*, 3*aS*, 6*aR*) Hexahydrofuro[2, 3-*b*]furan-3-yl-*N*-(*1S, 2R*)-1-benzyl-3-(cyclopentyloxy)(2-[(methylsulfonyl)amino]benzimidazol-5-ylsulfonyl)amino-2-hydroxypropyl carbamate;

5 (3*R*, 3*aS*, 6*aR*) hexahydrofuro[2, 3-*b*]furan-3-yl *N*-(*1S, 2R*)-3-[(*3*-N-methylaminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate;

10 1,3-Dioxan-5-yl *N*-(*1S, 2R*)-1-benzyl-3-[(cyclopentyloxy)(2-[(methoxycarbonyl)amino]-1*H*-benzimidazol-5-ylsulfonyl)amino]-2-hydroxypropylcarbamate;

15 (3*R*, 3*aS*, 6*aR*) hexahydrofuro[2, 3-*b*]furan-3-yl *N*-(*1S, 2R*)-1-benzyl-2-hydroxy-3-[(*4*-methoxyphenyl)sulfonyl](tetrahydro-2*H*-pyran-4-yloxy)amino]propylcarbamate;

20 (3*R*, 3*aS*, 6*aR*) hexahydrofuro[2, 3-*b*]furan-3-yl *N*-(*1S, 2R*)-3-[(*3*-aminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate;

25 (3*R*, 3*aS*, 6*aR*) hexahydrofuro[2, 3-*b*]furan-3-yl *N*-[(*1S, 2R*)-1-benzyl-3-((cyclopentyloxy)[3-(2-[methoxy(methyl)amino]-2-oxoethylamino)phenyl]sulfonylamino)-2-hydroxypropyl]carbamate;

30 (3*R*, 3*aS*, 6*aR*) hexahydrofuro[2, 3-*b*]furan-3-yl *N*-[(*1S, 2R*)-1-benzyl-3-(cyclopentyloxy)[(*4*-methoxyphenyl)sulfonyl]amino-2-hydroxypropyl]carbamate;

35 (3*R*, 3*aS*, 6*aR*) hexahydrofuro[2, 3-*b*]furan-3-yl *N*-[(*1S, 2R*)-1-benzyl-3-((cyclopentyloxy)[3-(2-[(methylsulfonyl)amino]ethylamino)phenyl]sulfonylamino)-2-hydroxypropyl]carbamate;

40 (3*R*, 3*aS*, 6*aR*) hexahydrofuro[2, 3-*b*]furan-3-yl *N*-(*1S, 2R*)-3-[(*3*-N-methylaminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate, phosphate ester;

45 (3*R*, 3*aS*, 6*aR*) hexahydrofuro[2, 3-*b*]furan-3-yl *N*-(*1S, 2R*)-3-[(*3*-aminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate phosphate ester;

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(3R,3aS,6aR) hexahydrofuro [2,3-b]furan-3-yl N-(1S,2R)-3-[(4-aminophenyl)sulfonyl](cyclopentyloxy)amino]-1-benzyl-2-hydroxypropyl carbamate;

5 (3R,3aS,6aR) hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-benzyl-3-[(1-ethylpropoxy)[(4-hydroxyphenyl)sulfonyl]amino]-2-hydroxypropylcarbamate;

(3R,3aS,6aR) hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(1-ethylpropoxy)amino]-1-benzyl-2-hydroxypropylcarbamate;

10 (3R,3aS,6aR) hexahydrofuro[2,3-b]furan-3-yl N-[(1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(cyclopentyloxy)amino]-1-benzyl-2-(phosphonoxy)propyl]carbamate;

15 (3R,3aS,6aR) hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(cyclohexyloxy)amino]-1-benzyl-2-hydroxypropylcarbamate;

(3R,3aS,6aR) hexahydrofuro[2,3-b]furan-3-yl 3-[(1,3-benzodioxol-5-ylsulfonyl)(tetrahydro-2H-pyran-4-yloxy)amino]-1-benzyl-2-hydroxypropylcarbamate;

20 (3R,3aS,6aR) hexahydrofuro[2,3-b]furan-3-yl N-[(1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(cyclopentyloxy)amino]-1-benzyl-2-(phosphonoxy)propyl]carbamate;  
or a pharmaceutically acceptable derivative thereof.

25 15. The compound according to claim 1 wherein  
said compound has a molecular weight less than or equal to  
about 700 g/mol.

30 16. The compound according to claim 15 wherein  
said compound has a molecular weight less than or equal to  
about 600 g/mol.

17. A pharmaceutical composition comprising an  
effective antiviral amount of a compound according to any  
one of claims 1-14 or a pharmaceutically acceptable

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derivative thereof together with a pharmaceutically acceptable carrier therefore.

18. The pharmaceutical composition according to  
5 claim 17, further comprising an antiviral agent other than a compound according to claims 1-14.

19. A pharmaceutical composition according to  
claim 17 or 18 in the form of a tablet or capsule.

10 20. A method of treating a virus infection in a human comprising administering to said human an effective antiviral treatment amount of a compound according to any one of claims 1-13 or a pharmaceutically acceptable  
15 derivative thereof.

21. The method according to claim 20 wherein the virus infection is an HIV infection.

20 22. The method according to claim 20 or 21 wherein said step of administering comprises oral administration or administration by injection.

25 23. Use of a compound according to any of claims 1-14 for the manufacture of a medicament for the treatment or prophylaxis of a viral infection.

30 24. Use of a compound according to any of claims 1-14 or a formulation according to claim 17 for use in medical therapy.

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(21) International Application Number: **PCT/US99/13744**

(74) Agents: **HALEY, James, F., Jr.; Fish & Neave, 1251 Avenue of the Americas, New York, NY 10020 et al.** (US).

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

**WO 99/65870 A3**

(54) Title: **SULFONAMIDE INHIBITORS OF ASPARTYL PROTEASE**

(57) Abstract: The present invention relates to a novel class of sulfonamides which are aspartyl protease inhibitors. In one embodiment, this invention relates to a novel class of HIV aspartyl protease inhibitors characterized by specific structural and physicochemical features. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting HIV-1 and HIV-2 protease activity and consequently, may be advantageously used as anti-viral agents against the HIV-1 and HIV-2 viruses. This invention also relates to methods for inhibiting the activity of HIV aspartyl protease using the compounds of this invention and methods for screening compounds for anti-HIV activity.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 99/13744

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C311/48 C07D235/30 C07D309/12 C07D309/06 C07D307/20  
C07D493/04 C07D215/48 C07D405/12 A61K31/27 A61K31/34  
A61K31/395

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C C07D A61K C09F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 05639 A (VERTEX PHARMACEUTICALS INC) 17 March 1994 (1994-03-17) claims 1-12, 16-24	1,15-24
A	WO 96 33187 A (VERTEX PHARMACEUTICALS INC) 24 October 1996 (1996-10-24) claims	1,15-24
A	WO 96 33184 A (VERTEX PHARMACEUTICALS INC) 24 October 1996 (1996-10-24) claims	1,15-24

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
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- \*O\* document referring to an oral disclosure, use, exhibition or other means
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- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- \*&\* document member of the same patent family

Date of the actual completion of the international search

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**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

**Continuation of Box I.2**

Claim 13 relates to 9 different structural entities of which only one is covered by general formula I of claim 1. The structures that are not covered by formula I are also not supported by the description. Consequently the search has not been pertinent to the structures in question.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/13744

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**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

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